TOWARDS THE TOTAL SYNTHESIS OF LYSERGIC ACID VIA A RHODIUM-CATALYZED ENANTIOSELECTIVE DESYMMETRIZATION OF SUBSTITUTED OXABICYCLES AND THE CONSTRUCTION OF TETRASUBSTITUTED HELICAL ALKENES BY A PALLADIUM-CATALYZED DOMINO PROCESS

by

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for the degree of Master of Science

Department of Chemistry
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Towards the Total Synthesis of Lysergic Acid via a Rhodium-Catalyzed Enantioselective Desymmetrization of Substituted Oxabicycles and the Construction of Tetrasubstituted Helical Alkenes by a Palladium-Catalyzed Domino Process

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Abstract

A synthetic approach to produce lysergic acid by virtue of an asymmetric ring opening (ARO) of symmetrical 3,6-disubstituted-7,10-hydroxymethyl bridgehead substituted oxabicycles is described. The use of a Rhodium(I)/JosiPhos(*R*,*S*) catalyst system to effect an ARO using an amine nucleophile furnishes an enantiopure tetrahydronapthalene intermediate with the amine conveniently installed at the 6 position as in lysergic acid, with appropriate stereochemistry; further which, two subsequent annulations are necessary to form the fused 3,5-substituted indole and tetrahydropyridine to complete the synthesis. Progress of this work is described herein along with future directions. The second chapter in this thesis describes the modular and stereoselective synthesis of tetrasubstituted helical alkenes via a palladium-catalyzed domino reaction under Catellani conditions. These helical alkenes possess potentially interesting photochemical properties as molecular motors / switches, and can be applicable in the materials sciences as molecular machines.

In memory of Keith Fagnou
(1971 – 2009)

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Fantastic 5, Dave P, Dave C, Jane, Steve, Gavin, Harald, Juliane, Patrick F, Dennis, Adam, Richard and Zafar – thanks for the regular company during lunch / dinner / movies / sports / Wonderland. The list could go on, including those from other labs, but for brevity's sake – I'd like to thank everyone else in the lab and department not mentioned here, present or past, for sharing this experience with me. Thanks for the great memories, and I hope we ensure that Chan's dog drawings never show up on our blackboards and fumehoods again.

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Stay tuned for more, I'll be back…

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List of Abbreviations

%	percent
Ac	acetyl
aq.	aqueous
ARO	asymmetric ring opening
ATP	adenosine triphosphate
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binapthyl
BMIM	1-butyl-3-methylimidazolium
Bn	benzyl
br	broad
brsm	based on reacted starting material
Bz	benzoyl
cat.	catalyst
CBS	Corey-Bakshi-Shibata
$CHCl_3$	chloroform
cod	1,5-cyclooctadiene
C_s	C_S point symmetry
CSA	camphorsulfonic acid
cm^3	cubic centimeter
D	deuterium
DA	Diels-Alder
DCE	1,2-dichloroethane
DCM	dichloromethane
dmdba	dimethoxydibenzylideneacetone
DMF	dimethylformamide
dppf	1,1’-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
E_{act}	activation energy
equiv.	equivalent
er	enantiomeric ratio
ee	enantiomeric excess

ESI	electrospray ionization
EtOAc	ethyl acetate
h	hour
HFIP	hexafluoroisopropanol
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
^{i}Pr	isopropyl
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
LG	leaving group
LTMP	lithium 2,2,6,6-tetramethylpiperidine
m	*meta*
M	molar
m.p.	melting point
mg	milligram
MHz	megahertz
mL	milliliter
mmol	millimoles
MW	microwave
n-Bu	butyl
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
Ns	nosyl
Nu	nucleophile
o	*ortho*
^{o}C	degrees Celsius
p	*para*
Pd	palladium
Ph	phenyl
PHOX	phosphinooxazoline
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl

PPh_3	triphenylphosphine
RaNi	Raney nickel
RCM	ring closing metathesis
Rh	rhodium
rt	room temperature
^{t}Bu	*tert*-butyl
sat.	saturated
ssDNA	single-stranded DNA
TBS	*tert*-butyldimethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
TFE	trifluoroethanol
TFP	tris(2-furyl)phosphine
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
$TMSCHN_2$	trimethylsilyldiazomethane
TosMIC	toluenesulfonylmethyl isocyanide
α	alpha
β	beta
δ	chemical shift or delta
η	eta

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Chapter 1

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Chapter 1: Towards the Total Synthesis of Lysergic Acid

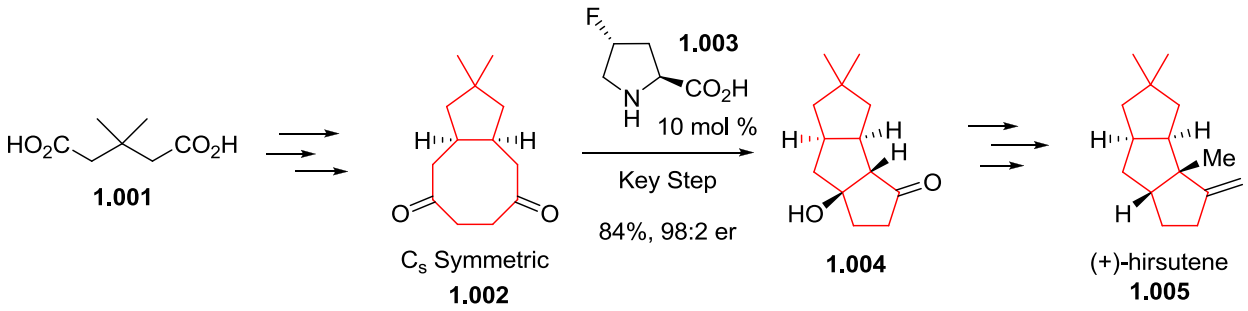
1.1 Introduction

1.1.1 Symmetry in Synthetic Planning

The utility of a molecule's symmetry in the synthesis of a complex target is by no means an intuitive approach. When applied, it can be the most rewarding strategy in accessing molecular complexity in a facile manner. The use of symmetrical intermediates allows for a high degree of control in that desymmetrization reactions can yield either asymmetric product of choice depending on the method used to favour a particular enantiotopic face. Moreover, as large symmetrical building blocks can be made readily, synthetic routes using these intermediates can be more efficient than convergent syntheses as fewer steps are needed for the preparation of one substrate as opposed to two separate building blocks.

A recent example by List and co-workers' highlighs the use of symmetry in the total synthesis of (+)-hirsutene[1] **1.005** (Scheme 1-1). Bis-substituted alkyl carboxylic diacid **1.001** is modified to provide *syn* (8,5)-fused-cyclooctanedione **1.002** with C_s point group symmetry. This intermediate is then subjected to an asymmetric transannular aldol as the key step using chiral

Scheme 1-1 Total synthesis of (+)-hirsutene highlighting key organocatalytic step

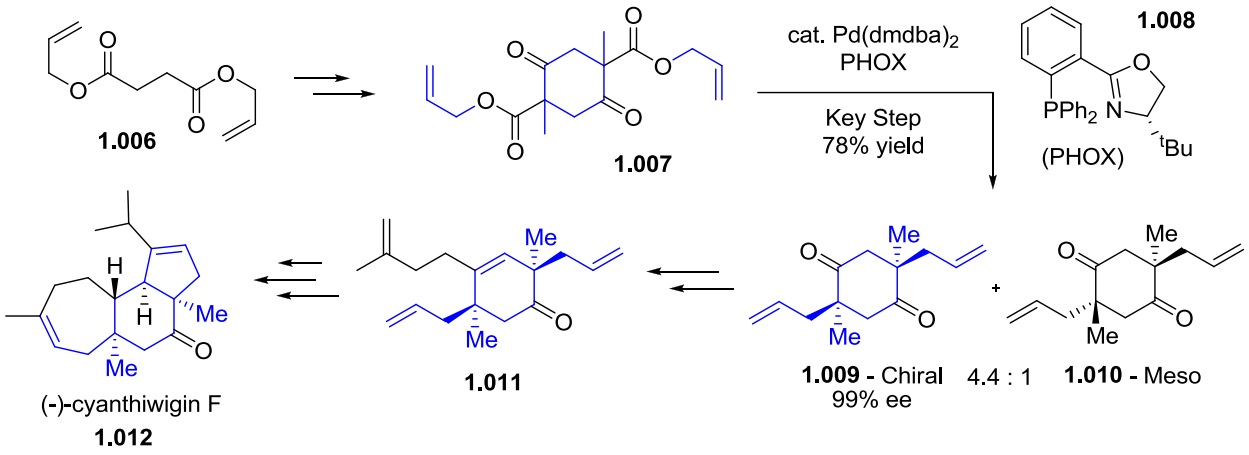


[1] Chandler, L.C.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6737-6739.

proline **1.003** to provide the (5,5,5)-fused ring core **1.004** of the natural product in 84% yield and 98:2 er. Further manipulation, including elimination of the tertiary alcohol to the enone, Birch reduction of the Michael system with trapping of MeI, and Wittig olefination, furnishes the natural product **1.005** in 13 steps with an overall yield of 6.6%. This synthesis demonstrates the effectiveness of planning an asymmetric step on a symmetric intermediate as close to all the carbon atoms found in the target, highlighted in red, are derived from **1.002**. Thus, (+)-hirsutene was accessed in fewer steps than the previously reported asymmetric syntheses.[2]

Stoltz and coworkers also features the use of symmetry in their total synthesis of (-)-cyanthiwigin F **1.012** (Scheme 1-2).[3] Starting with diallyl succinate **1.006**, a Claisen-Dieckmann self-condensation is done followed by methylation to furnish a diastereomeric mixture (1:1 [*R*,*R*]&[*S*,*S*] : meso [*R*,*S*]) of the cyclohexanedione succinyl intermediate **1.007**. A Pd-catalyzed double decarboxylative alkylation using chiral PHOX ligand **1.008** as the key step affords bis-alkylated **1.009** and *meso*-**1.010** as a 4.4:1 mixture in a 78% yield, respectively. This step is quite elegant in that a chiral product is resolved from a stereosiomeric mixture. This is achieved by

Scheme 1-2 Total synthesis of (-)-cyanthiwigin F highlighting Pd-catalyzed decarboxylative alkylation



[2] Previous reports of asymmetric total syntheses of hirsutene include: (a) Hua, D. H.; Venkataraman, S.; Sinai-Zingde, G. *J. Am. Chem. Soc.* **1985**, *107*, 4088. (b) Weinges, K.; Reichert, H.; Huber-Patz, U.; Irngartinger, H. *Liebegs Ann. Chem.* **1993**, 403. (c) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A. *Tetrahedron* **2004**, *60*, 535.

[3] Enquist, J.A. Jr.; Stoltz, B.M. *Nature* **2008**, *453*, 1228.

multiple stereoablations of each succinyl group, followed by bond construction of the allyl group. From the mixture of starting materials, one can imagine 16 different pathways to result with any of three stereoisomers (**1.009**, **1.010** and en-**1.009** – not shown). Stoltz attributed the stereoconvergence to **1.009** as the catalyst system's capacity to impart a high degree of control to select for **1.009**, by funneling all the intermediates to it. A diagram illustrating this explanation is found in the referenced manuscript. The authors then derivatize one of the homotopic ketones in **1.009** to introduce the olefinic side chain **1.011**; after which, RCM is done to form the (7,6) fused-ring system in the current stereochemistry. Additional modifications of the frontier intermediate, including a radical cyclization to annulate the 5 membered ring, provided the natural product **1.012** in 9 steps with an overall yield of 1.3%. A large segment of the target, highlighted in blue, is derived from **1.007** early into the synthesis and this is owed to the ease of accessing large symmetrical building blocks.

Many more examples of using symmetry as a strategy have been used in total synthesis.[4] Scheme 1-3 illustrates selected examples of recent and classic total targets[5] involving symmetrical or pseudo-symmetrical substrates. These examples highlight the variety of methods applied to symmetrical compounds in total synthesis, including a stereoselective Diels Alder, an enzymatic desymmetrization, an asymmetric domino reaction, to name a few. In general, this strategy proves to be versatile in synthesis given the complexity of the targets that have been accessed, along with the added benefits of pursuing such routes in that they are remarkably efficient. However, it is difficult to employ in synthesis as it can be a challange to decide upon a symmetrical synthon without an already established method to desymmetrize it into a useful chiral intermediate.

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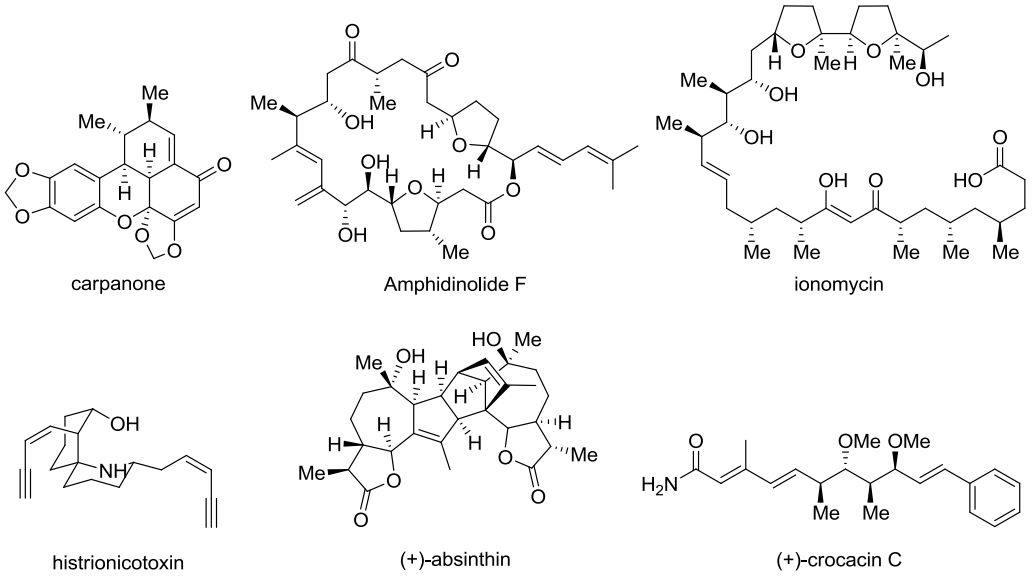
[4] (a) "Symmetry: A Basis for Synthetic Design" Tse-Lok Ho. Wiley-Interscience: **1995**, 584 pages. (b) A review on the "Art and Science of Total Synthesis" by Nicolaou, K.C., et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 44-122 highlights some targets accessed by symmetrical means. (c) "The Way of Synthesis" Hudlicky, T. and Reed, J.W. Wiley-VCH: **2007**, 1018 pages. (d) "Classics in Stereoselective Synthesis" Carreira, E.M. and Kvaerno, L. Wiley-VCH: **2009**, 651 pages.

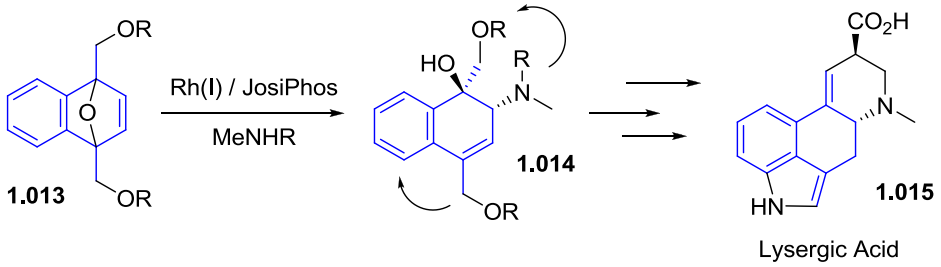
[5] For the interested reader, the references to the total syntheses mentioned are as follows: (a) carpanone: Chapman, O.L. et al. *J. Am. Chem. Soc.* **1971**, *93*, 6696. (b) Amphidinolide F: Mahapatra, S.; Carter, R.G. *Angew. Chem. Int. Ed.* **2012**, *51*, 7948. (c) ionomycin: Lautens, M.; Colucci, J. T., et al. *Org. Lett.* **2002**, *4*, 1879. (d) histrionicotoxin: Fuchs, P.L; Stockman, R.A. et al. *J. Am. Chem. Soc.* **2006**, *128*, 12656. (e) (+)-absinthin: Hongbin, Z.; Zhang, W., et al. *J. Am. Chem. Soc.* **2005**, *127*, 18. (f) (+)-crocacin C: Pons, J-M.; Bressy, C., et al. *J. Org. Chem.* **2010**, *75*, 1354.

Scheme 1-3 A selection of targets synthesized using symmetrical intermediates



Our aim is to synthesize lysergic acid **1.015** enantioselectively by means of a Rh-catalyzed asymmetric ring opening reaction (ARO) of a meso-bridgehead substituted oxabenzonorbornadiene **1.013** (Scheme 1-4). This ring-opening is done using an amine nucleophile to prepare a dihydronaphthalene core with the amine substituent oriented in the correct stereochemistry **1.014**. Thereafter, two annulations are planned to construct the indole ring and the tetrahydropyridine to form the tetracyclic fused-ring system. This novel approach towards the formation of **1.015** could prove to be an elegant strategy given the large symmetrical intermediate used. Furthermore, this method would be a useful addition to the diverse array of symmetrical building blocks which have been desymmetrized in total syntheis.

Scheme 1-4 Proposed key step towards the enantioselective synthesis of lysergic acid



1.1.2 Background on Lysergic Acid

Lysergic acid is a precursor of the ergoline alkaloids produced by the ergot fungus and some plants. It is formed by the hydrolysis of these natural products, such as ergotamine **1.016** (Scheme 1-5). The ergoline alkaloid is commonly characterized by a tetracyclic-fused core bearing an indole moiety (rings **A**-**B**), a cyclohexyl ring (**C**), and a dihydropiperidine (**D**). This class of compounds is revered to be the most potent family of natural products.[6] The biological activity was first identified historically as early as the 12th century when people contracted 'ergotism' or 'St. Anthony's Fire' from fungus infected rye, crediting the monks of the Order of St. Anthony who were successful at treating this ailment. Symptoms included hallucinations, convulsions, and gangrene.

This molecule is also infamously known for its psychedelic properties by its recreational use as a hallucinogen, and lysergic acid diethylamide or LSD **1.019** is the molecule known for this. Initially introduced as a drug by Albert Hofmann in 1938 after the first semisynthesis from ergotamine, along with Hofmann's personal account of its ingestion in 1943,[7] LSD found its real application in the 'turn on, tune in and drop out' culture in the 1960s before its prohibition after much political revolt. It is no wonder that the discovery of LSD has had an enormous impact on neuroscience research and medicine given its potency, at 20-30 μg being the threshold dose.[8] Other derivatives have been implicated in the treatment of other medical ailments **1.017 – 1.018** and **1.020 – 1.022** (Scheme 1-5), most notably in Parkinson's disease. Thus, given the large degree of bioactivity, the ergoline alkaloids have been the subject of many synthetic studies with the aim to create novel compounds for the purpose of biological testing to discover future medical treatments.

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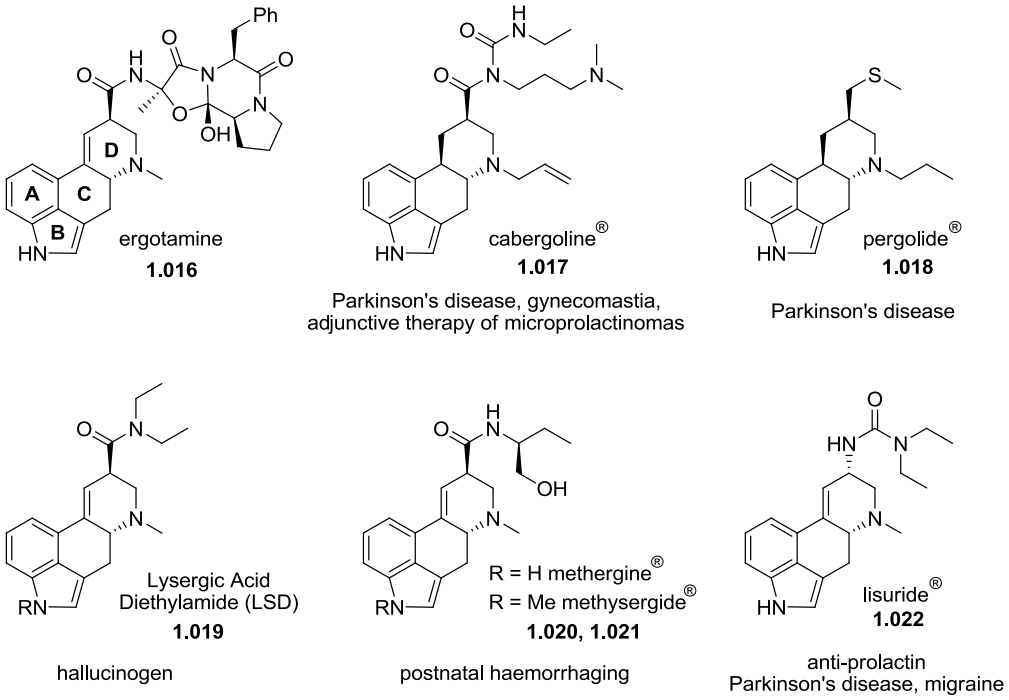
[6] "The Alkaloids" M. Somei, Y. Yokoyama, Y. Murakami, I. Ninomiya, T. Kiguchi, T. Naito (Ed. G. A. Cordell), Academic Press: San Diego, CA, **2000**.

[7] "LSD – My Problem Child" Hofmann, A. (Trans. Ott. J.) McGraw-Hill: New York, **1980**, 209 pages.

[8] Greiner, T.; Burch, N.R.; Edelberg, R. *AMA Arch Neurol Psychiatry* **1958**, *79*, 208.

Scheme 1-5 Analogues of lysergic acid found in nature and medicine

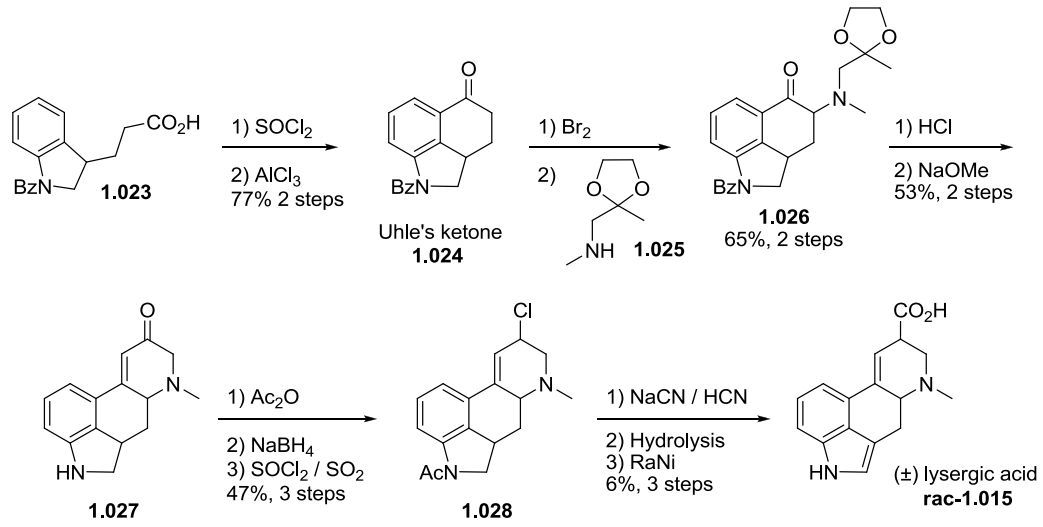


The first synthesis of the lysergic acid scaffold was reported by Uhle and Jacobs in 1945.[9] Thereafter, several syntheses of **1.015** and its analogues proceeded via 'Uhle's ketone' **1.024** as shown in the first total synthesis by Woodward and coworkers[10] of racemic **1.015** in 1954 (Scheme 1-6). The synthesis uses a 3-propanoic acid benzyl protected indoline **1.023** as the starting material, requiring two subsequent six-membered ring annulations to prepare the fused tetracyclic ergoline backbone. The indoline motif contains a large segment of the desired target, and its use is part of a recurring theme in syntheses following Woodward's.

[9] Uhle, F.C.; Jacobs, W.A. *J. Org. Chem.* **1945**, 176.

[10] Woodward, R.B.; Kornfeld, E.C., et al. *J. Am. Chem. Soc*. **1954**, 5256; *J. Am. Chem. Soc.* **1956**, 3087.

Scheme 1-6 Woodward's total synthesis of (±)-**1.015**



The first asymmetric synthesis of **1.015** was reported by Szántay and coworkers (Scheme 1-7).[11] A chiral resolution was done on advanced intermediate **1.027** derived from Uhle's ketone, prepared analogously to Woodward's synthesis using 3-indolepropionic acid by Goto's improved method.[12] Using (-)-dibenzoyl-L-tartaric acid, **1.027** was resolved to provide optically active **1.029**. The stereochemistry was established by degradation of natural lysergic acid[13] to compare the absolute configurations. **1.029** was functionalized as a formamide by treatment of TosMIC, and base hydrolysis afforded a racemic mixture of nitriles. The mixture was then converted into the methyl esters by a Pinner reaction to give **1.030** in a 3:2 (+/-) dr. Subsequent base hydrolysis of the mixture resulted in pure **1.015** after epimerization.

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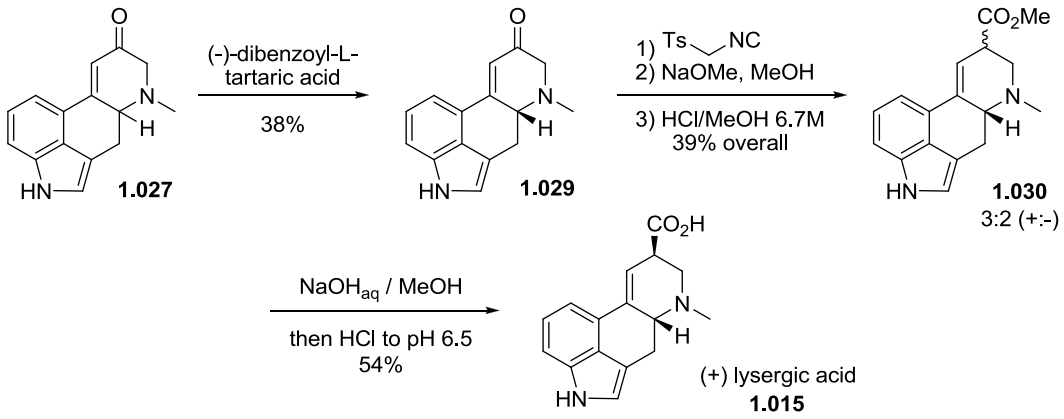
[11] Moldvai, I., Temesvári-Major, E.; Incze, M.; Szentirmay, É.; Gács-Baitz, E.; Szántay, C. *J. Org. Chem.* **2004**, 69, 5993.

[12] Teranishi, K.; Hayashi, S.; Nakatsuka, S.; Goto T. *Tetrahedron Lett.* **1994**, *35*, 8173.

[13] (a) Bernardi, L.; Gandini, E.; Temperilli, A. *Tetrahedron* **1974**, *30*, 3447. (b) Bach, N. J.; Kornfeld, E.C. *Tetrahedron Lett*. **1974**, 3225.

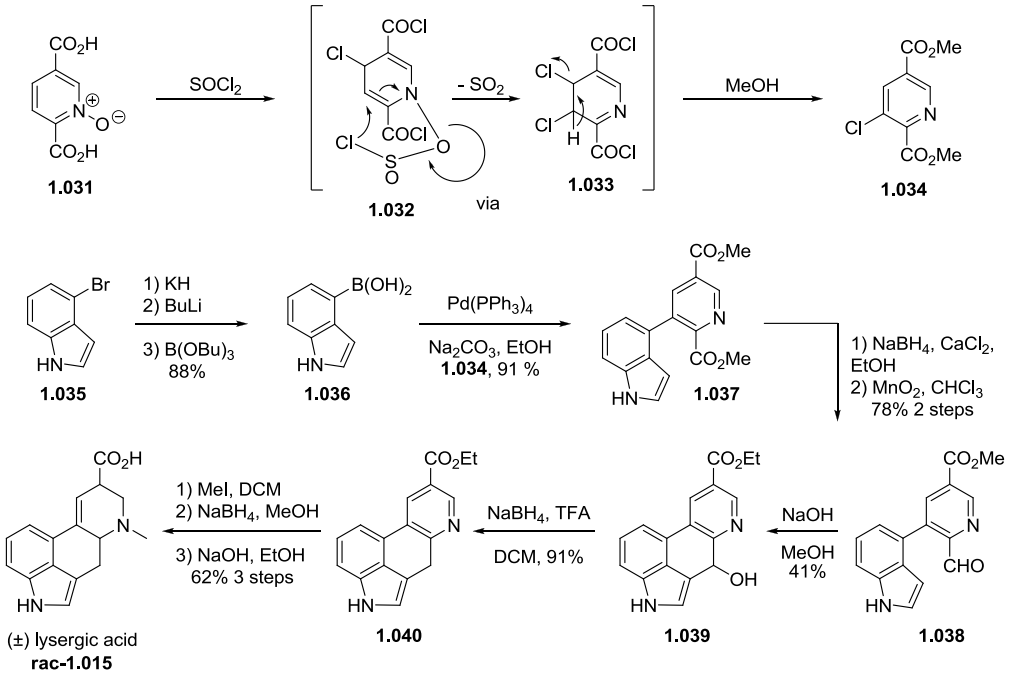
Scheme 1-7 First enantioselective synthesis of **1.015** by Szántay



Following this report, Hendrickson and coworkers published a racemic synthesis[14] of **1.015** with a short synthetic sequence (Scheme 1-8). Bromide **1.035** was converted into boronic acid **1.036**. Subsequent Suzuki coupling of indole **1.036** with chloride **1.034** afforded intermediate **1.037**, bearing an ester group within proximity for an annulation. The preparation of coupling partner **1.034** is interesting as typical chlorinations of pyridine *N*-oxides are *ortho*/*para* selective. The *meta* product is formed by what the authors believe to be a pericyclic rearrangement of **1.032** to install the chlorine at the *meta* position **1.033**, and subsequent loss of the *para* chloride to afford **1.034** upon esterification. The α-picolinic ester was transformed to aldehyde **1.038**, which was then cyclized under basic conditions to form tetracyclic fused product **1.039**. Standard reductive manipulation to remove the alcohol, installation of the methyl group, reduction of the pyridine, and hydrolysis of the ester furnished racemic **1.015** in 8 steps from **1.036** and **1.034**. This was the first convergent synthesis without the need to protect the indole. Presently, **1.015** has not been synthesized more efficiently than Hendrickson's, setting the shortest sequence at 11 steps with an overall unoptimized yield of 10.6%.

[14] Hendrickson, J.B.; Wang, J. *Org. Lett.* **2004**, *6*, 3.

Scheme 1-8 Hendrickson's racemic synthesis of **1.015**



Other groups have contributed in recent years by changing the approach in which an indole was used to prepare **1.015** through a variety of methods. This includes, Ohno and coworkers racemic total synthesis[15] in 2008 by a Pd-catalyzed domino cyclization of amino allenes bearing a bromoindolyl group **1.041** (Scheme 1-9). The fused ergoline intermediate **1.042** is quickly assembled in one step to form the **C**/**D** rings in 65% yield with a dr of 88:12. The rationale for the selectivity is proposed by the authors' mechanism as illustrated in Scheme 1-9. They believe that the domino reaction can proceed in one of two pathways upon oxidative addition: through carbopalladation of **1.043** or amidopalladation of **1.045**. In the case of carbopalladative addition, sterics are believed to orient the indolylpalladium(II) bromide **1.043** for a 6-*exo* type cyclization to generate an η^3-allylpalladium complex **1.044**. This intermediate then undergoes a nucleophilic cyclization by the nosylamide in an *anti* elimination to furnish the minor isomer. Otherwise, diastereomeic species **1.045** can undergo an *anti* attack to construct both rings concertedly to generate 7-membered palladacycle **1.046**, which upon reductive elimination affords the major product. The bias of the major product is believed to be caused by the otherwise sterically hindered bicyclic transition state of **1.043**.

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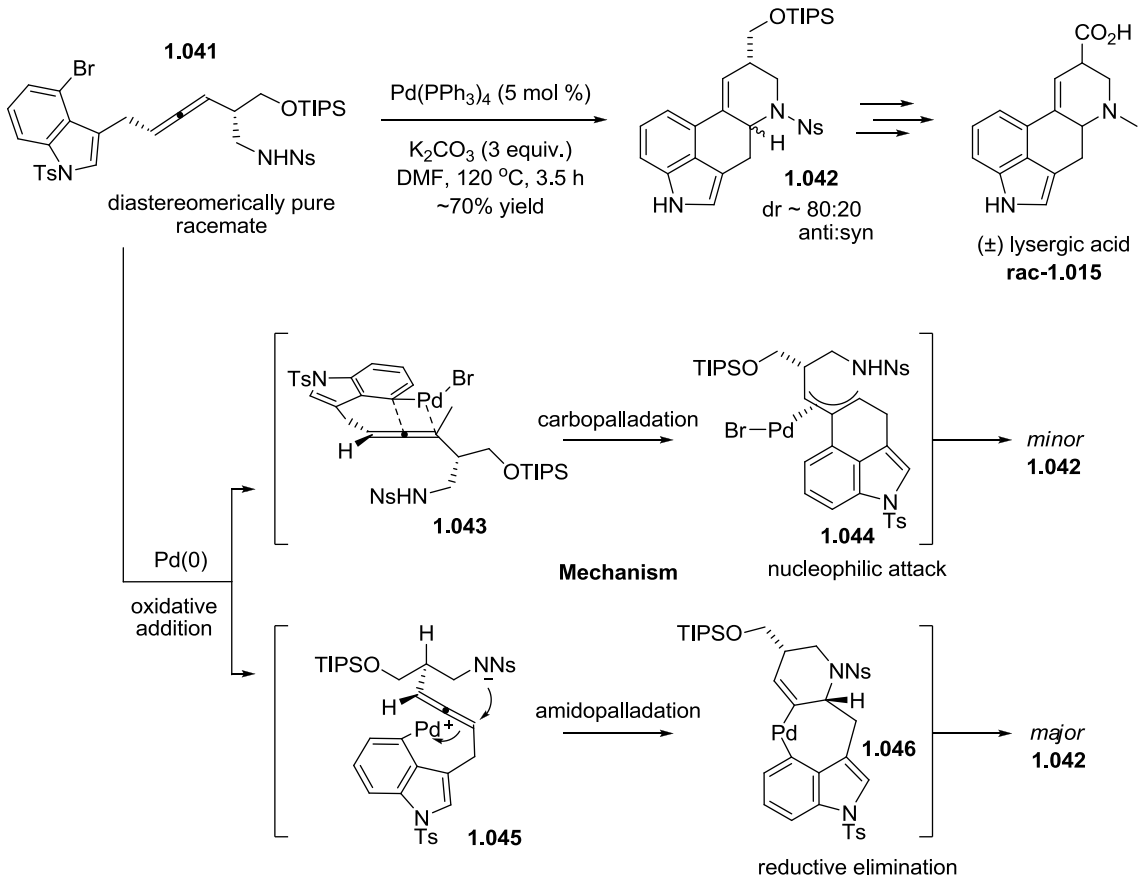
[15] Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 5239.

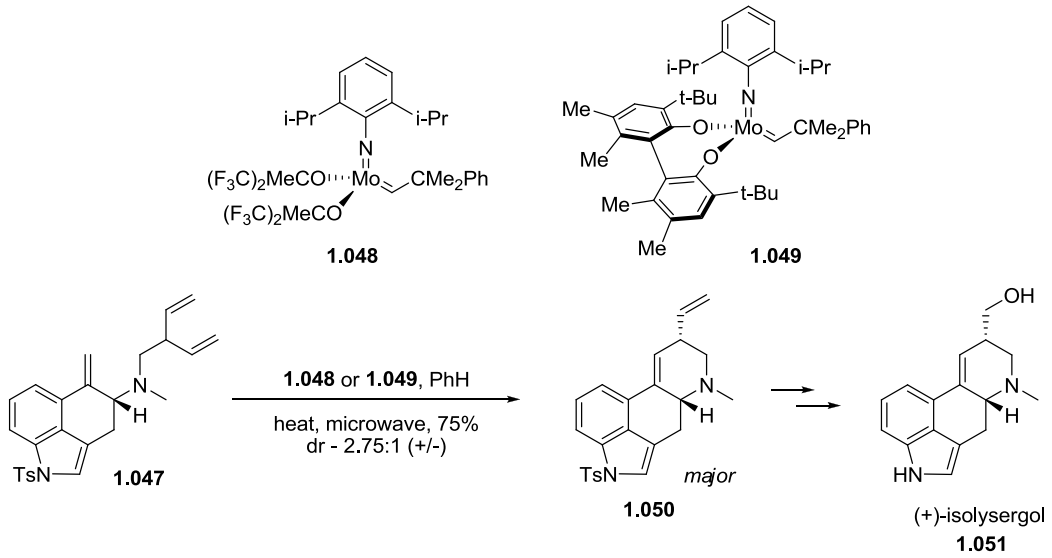
Scheme 1-9 Ohno's racemic synthesis of **1.015** highlighting key tandem catalytic step



In 2010, Martin and coworkers reported an enantioselective synthesis[16] of (+)-isolysergol **1.051**, a closely related member of the ergot family, via an asymmetric ring-closing metathesis of tricyclic fused triene **1.047** to construct the **D** ring **1.050** (Scheme 1-10). This was done using either the Schrock **1.048** or Schrock-Hoveyda catalyst **1.049** under microwave conditions to furnish the major diastereomer **1.050** in the appropriate stereochemistry at C5. Subsequent manipulations furnished **1.051**, which can be easily transformed into **1.015** by oxidation of the terminal alcohol to the carboxylic acid and epimerized as in Szántay's synthesis.

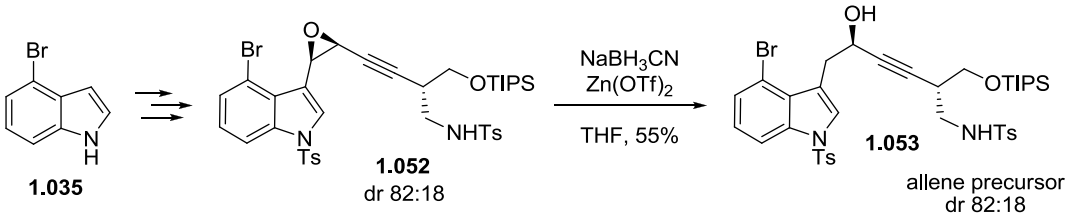
[16] Deck, J.A; Martin, S.F. *Org. Lett.* **2010**, *12*, 2610.

Scheme 1-10 Martin's synthesis of (+)-isolysergol using RCM



In 2011, Ohno and coworkers enantioselectively synthesized[17] **1.015** using the same domino method reported earlier. This was done by an improvement[18] in the preparation of enantiopure allene precursor **1.053** through a reductive ring-opening of a chiral indolyloxirane **1.052** with $NaBH_3CN$ as the key step. By using $Zn(OTf)_2$ as the additive, the ring-opening furnished the propargyl alcohol in good regioselectivity and diastereomeric excess (Scheme 1-11). The authors maintain the diastereoselectivity to arise from two potentially productive pathways, carbopalladative and aminopalladative, but they suggest that either diastereomer can proceed by aminopalladation and that one isomer is favoured over another due to conformational effects arising from steric interactions in the transition state.

Scheme 1-11 Ohno's updated preparation of chiral allene precursor

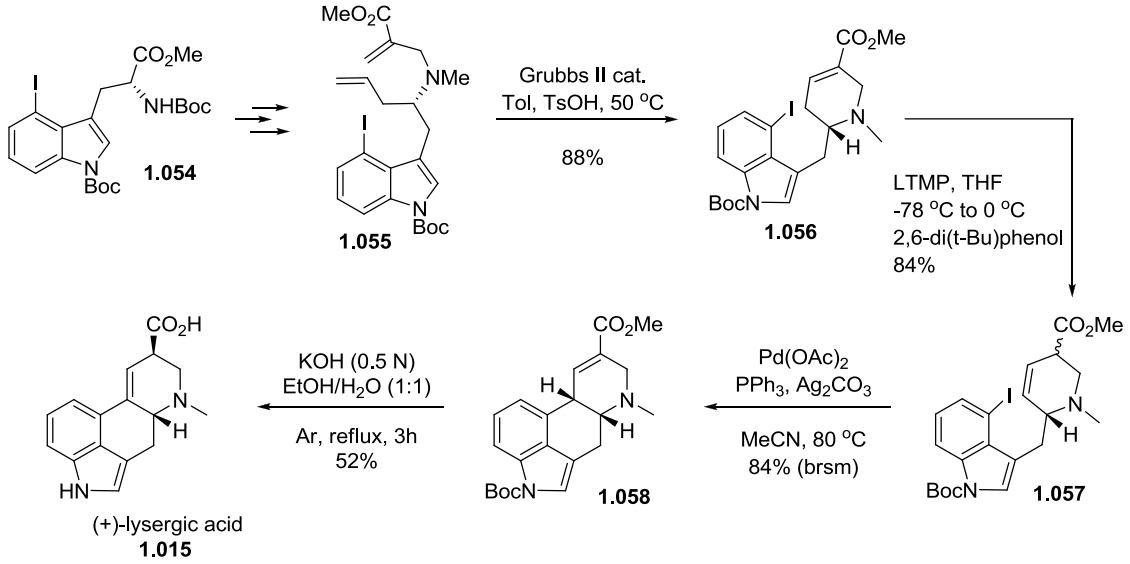


[17] Inuki, S.; Iwata, A.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 2072.

[18] Iwata, A.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 5506.

The same year, another asymmetric total synthesis of **1.015** was reported by Jia and coworkers[19] where they employed multiple metal-catalyzed methods for the construction of the **D** and **C** rings (Scheme 1-12). Starting from chiral iodotryptophan **1.054**, the diene intermediate **1.055** was prepared, followed by olefin metathesis using Grubb's second generation catalyst to prepare **1.056**. Isomerization of the double bond using LTMP and 2,6-di(t-Bu)-phenol as stabilizer liberated intermediate **1.057** for subsequent intramolecular Heck to give **1.058**. Lastly, base isomerization of the double bond, deprotection of Boc group, and hydrolysis of the ester furnished enantiopure **1.015**.

Scheme 1-12 Jia's total synthesis of (+)-**1.015**



Jia's synthetic strategy is an improvement of Fukuyama and coworkers[20] asymmetric synthesis in 2009, where they first introduced the idea of an intramolecular Heck coupling to construct the **C** ring; however, an elaborate starting material synthesis was necessary to prepare the functionalized **D** ring **1.062**. Double-cyclization precursor **1.060** was prepared convergently by conjugate-addition of **1.062** with lithiated species **1.061**. Additionally, the indole along with the **C** ring had to be formed in order to prepare **1.059**, which made the synthetic sequence lengthy (Scheme 1-13).

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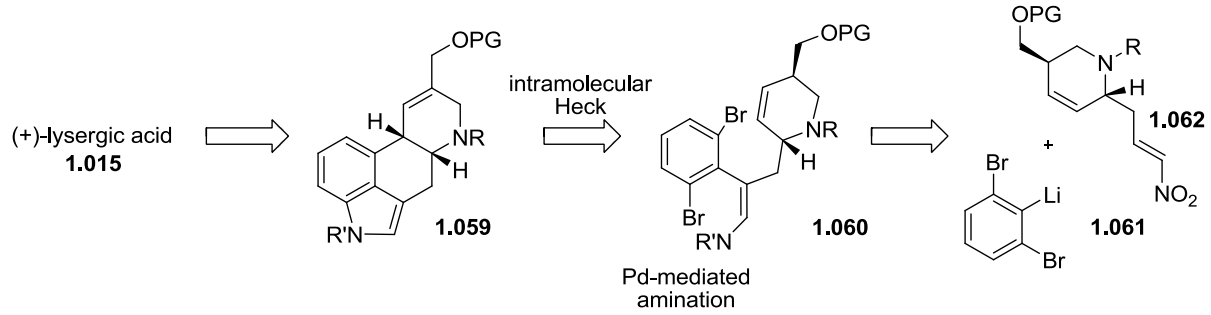
[19] Liu, Q.; Jia, Y. *Org. Lett.* **2011**, *13*, 4810.

[20] Kurokawa, T.; Isomura, M.; Tokuyama, H.; Fukuyama, T. *Synlett* **2005**, *5*, 775.

Scheme 1-13 Retrosynthetic route of Fukuyama's enantioselective synthesis of **1.015**



In all, there have been approximately 20 total syntheses of lysergic acid over the past 60 years. Interestingly, all of them arise from a functionalized indole or indoline as the starting material, to which the **C** and **D** rings are then annulated to form the ergoline skeleton. Of these, only four syntheses have been accomplished asymmetrically and there is increasing momentum in the research community to find better and efficient approaches to this molecule.

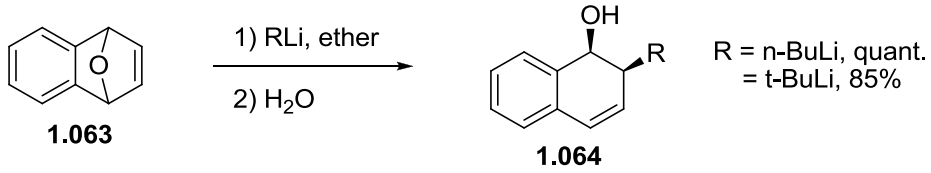
1.2 Introduction to Rh-Catalyzed Asymmetric Ring-Opening Reactions of [2.2.1] Oxabicyclic Alkenes

1.2.1 Background

Oxabicycles are a privileged class of molecules, serving as a precursor towards the formation of ring-opened products. As these molecules exhibit high ring strain,[21] the high potential energy is a driving force in these ring openings. The Lautens group has had a long-standing interest in ring-opening chemistry of strained, bicyclic molecules. Specifically, the ring-opening reactions of strained [3.2.1] and [2.2.1] oxabicyclic alkenes have been intensely investigated, wherein the ring strain is relieved by eliminating the bridging carbon-oxygen bond. Several enantioselective transition metal-catalyzed methods have been applied onto these substrates to form highly valuable asymmetric products. The aim of this section is to highlight a selection of methods used to form highly valuable compounds for the purposes of total synthesis.

In 1971, Caple and coworkers[22] set the precedent for ring-opening reactions of benzofused [2.2.1] oxabicyclic alkene **1.063** using organolithium nucleophiles, to yield alkylated **1.064** with exo selectivity (Scheme 1-14). 20 years later, this chemistry was revisited by the Lautens group in their first ring-opening reaction of a [3.2.1] oxabicyclic alkenes using cuprate nucleophiles.[23] Concurrently, Plumet and coworkers studied the ring-opening of [2.2.1] systems with organolithiums.[24] Lautens found that the less strained [3.2.1] systems were not as reactive

Scheme 1-14 First reported ring-opening of benzofused oxabicyclic alkenes



1.063 **1.064**

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[21] "*Modern Physical Organic Chemistry*" Anslyn, E.; Dougherty, D. University Science Books: **2006**, pp. 109-112.

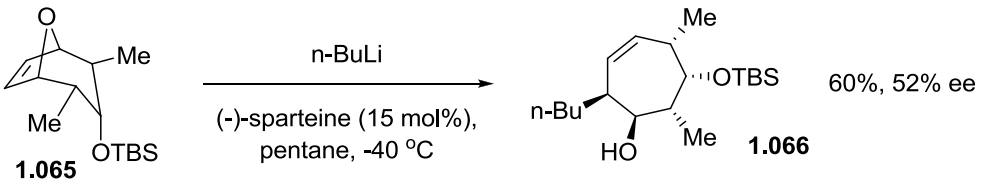
[22] Caple, R.; Chen, G.; Nelson, J. *J. Org. Chem.* **1971**, *36*, 2874.

[23] (a) Lautens, M.; Di Felice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, *30*, 6817. (b) Lautens, M.; Smith, C.; Abd-El Aziz, A.; Huboux, A. *Tetrahedron Lett.* **1990**, *31*, 3253; for reviews see: (c) Lautens, M. *Synlett* **1993**, 177. (d) Woo, S.; Keay, B. *Synthesis* **1996**, 669. (e) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, pp. 1-85.

[24] Plumet, J.; Arjona, O., et al. *Tetrahedron Lett.* **1989**, *30*, 6437; *Tetrahedron Lett.* **1990**, *46*, 8187.

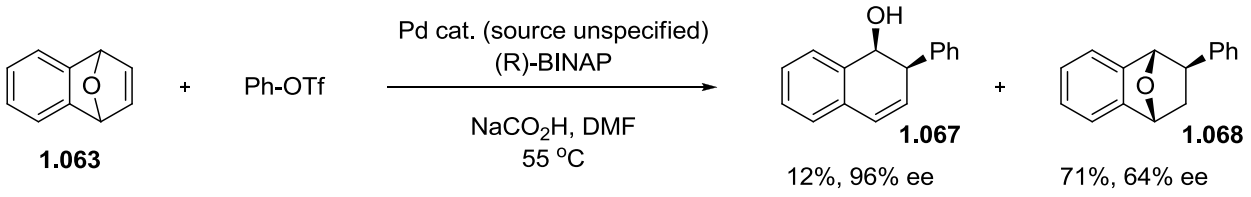
towards nucleophilic addition with methyllithium, requiring TMEDA additive to accelerate the alkylative ring-opening.[25] This led to their discovery of the first asymmetric ring-opening reaction of an oxabicyclic alkene. Lautens had opened [3.2.1] bicycle **1.065** in the presence of catalytic (-)-sparteine to generate cycloheptene **1.066**, setting five contiguous stereocenters simultaneously in modest *ee* (Scheme 1-15).[26]

Scheme 1-15 First asymmetric ring-opening of an oxabicyclic alkene



Following this, Moinet and Fiaud reported the first highly enantioselective transition metal-catalyzed desymmetrization of [2.2.1] benzofused oxabicyclic alkene **1.063** (Scheme 1-16).[27] Using a Pd catalyst in conjunction with (*R*)-BINAP, phenyl triflate reacted with **1.063** to yield two products, a ring opened product **1.067** and an addition product **1.068**. **1.067** was obtained as the minor product formed by carbopalladation/β-oxygen elimination in 12% yield and 96% ee. The major product was **1.068** was formed via a carbopalladation/reduction sequence in 71% yield and 64% ee. Interestingly, when phenyltriflate was substituted for iodobenzene, the selectivity reversed to give **1.067** as the major product with no induced enantioselectivity.

Scheme 1-16 First transition metal catalyzed asymmetric ring-opening of an oxabicyclic alkene



The reactions that followed thereafter included many efficient highly enantioselective catalytic systems developed for [3.2.1] and [2.2.1] oxa- and azabicyclic alkenes using a host of

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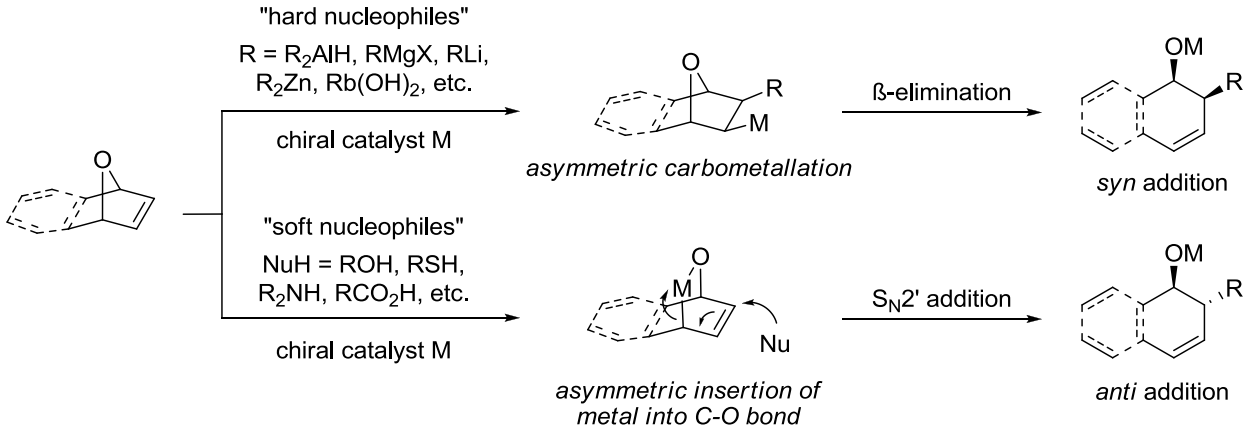
[25] Lautens, M.; Chiu, P. *Tetrahedron Lett.* **1993**, *34*, 773.

[26] Lautens, M.; Gadja, C.; Chiu, P. *Chem. Commun.* **1993**, 1193.

[27] Moinet, C.; Fiaud, J. *Tetrahedron Lett.* **1995**, *36*, 2051.

different metals and nucleophiles. Investigation in the Lautens' lab over the past two decades have revealed that nucleophilic ring-opening can proceed with differing stereochemical outcomes depending on the nature of the metal catalyst and nucleophile used. Lautens and Fagnou proposed two reaction mechanisms to account for this behaviour (Scheme 1-17). Diastereoselectivity is favoured *syn* for hard nucleophiles (RLi, Girgnard reagents, alkyl zinc, alkyl boronic acid) via an asymmetric carbometallation pathway, and *trans* for softer nucleophiles (alcohols, amines, thiols, malonates) via insertion of the metal catalyst into the bridging C-O bond followed by S_N2' addition.[28]

Scheme 1-17 Proposed mechanisms for various metal catalyzed ring-opening reactions



Various metals have been used in asymmetric ring-opening reactions, including Ti, Zr, Rh, Ir, Ni, Pd, and Cu. For the purposes of this project, only systems involving Rh catalysis is discussed, although more information on how the field matured can be found herein.[29]

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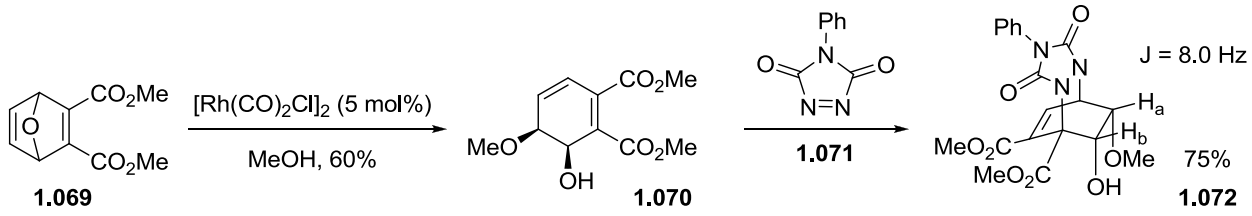
[28] For a review see: Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

[29] (a) Rayabarapu, D.; Cheng, C. *Acc. Chem. Res.* **2007**, *40*, 971. (b) Trost, B.; Van Vranken, D. *Chem. Rev.* **1996**, *96*, 395. (c) "Comprehensive Asymmetric Catalysis" Pfaltz, A.; Lautens, M. (Chapter 22, Vol II); Jacobsen, E.; Pfaltz, A.; Yamamoto, H., Eds.; Springer-Verlag: Berlin, **1999**, p833. (d) see ref. 27. (e) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (f) Webster, R., *Ph.D. Thesis*, University of Toronto, **2011**.

1.2.2 Rhodium Catalyzed Asymmetric Ring-Opening

The first ring-opening of a [2.2.1] oxabicyclic alkene system using a heteroatom nucleophile was reported by Hogeveen and Middlecoop (Scheme 1-18).[30] Oxabicyclic alkene **1.069** was treated with catalytic $[Rh(CO)_2Cl]_2$ in methanol to afford **1.070** in quantitative yield (according to ^{1}H NMR). The relative stereochemistry was later determined[31] to be *cis* by conversion of **1.070** to **1.072** via a Diels-Alder reaction with **1.071** and measurement of J_{Ha-Hb}.

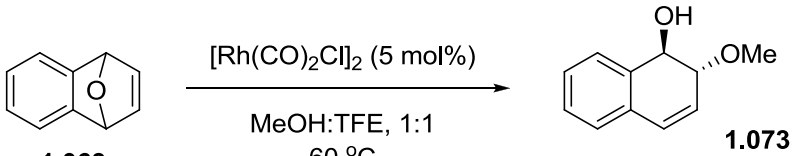
Scheme 1-18 Hogeveen and Middelkoop's methanolysis of an oxabicycle



1.069 **1.070** **1.072**

Inspired by their observations, a similarly designed Rh-catalyzed ARO was undertaken by Keith Fagnou and Tom Rovis during their doctoral studies in the Lautens group. Oxabicycle **1.063** was subjected to the same conditions to liberate ring opened **1.073** in 70% isolated yield with *trans* addition observed (Scheme 1-19).[32] It was necessary to use TFE as a co-solvent to better solubilize precipitates observed when using methanol alone.

Scheme 1-19 Application of Hogeveen and Middelkoop's conditions onto benzofused oxabicyclic alkenes



1.063 **1.073**

70%

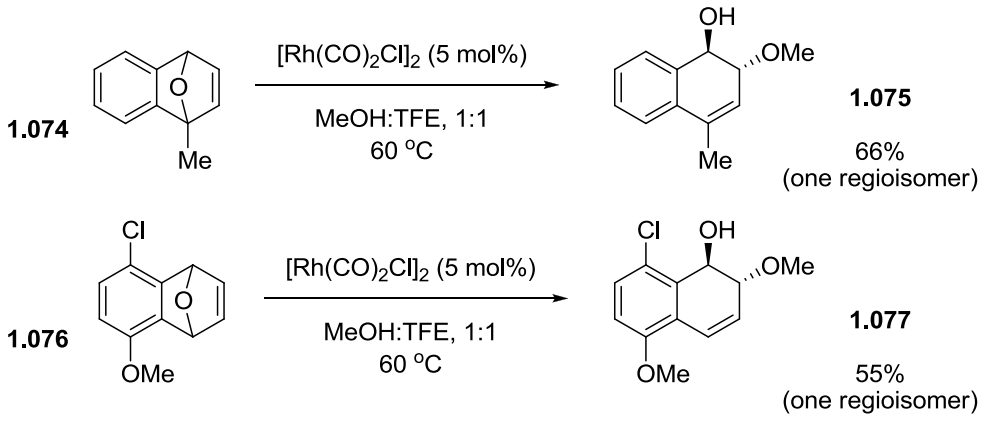
[30] Hogeveen, H.; Middelkoop, T. *Tetrahedron Lett.* **1973**, *14*, 3671.

[31] Ashworth, R.; Berchtold, G. *Tetrahedron Lett.* **1977**, *18*, 339.

[32] Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650.

Initial ring-opening studies using unsymmetrical oxabicyclic substrates **1.074** and **1.076** suggests an ionization mechanistic pathway, as each case only yielded one regioisomer when observing the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 1-20).[33] This regioselectivity was believed to arise from electronic bias of the C-O bond cleavage to give the more stable carbocation, to which the metal can insert itself between the two atoms.

Scheme 1-20 Regioselective methanolysis of unsymmetrical benzofused oxabicycles



Optimization of the reaction conditions determined $[Rh(cod)Cl]_2$ to be the optimal catalyst, as $[Rh(CO)_2Cl]_2$ tended to form precipitates when used with phosphine ligands. This screen also identified the planar chiral bidentate *tert*-Butyl-Josiphos ligand **1.078** (Scheme 1-21) to be most effective. It is using this catalyst/ligand system that the first generation conditions for this reaction was developed (Scheme 1-21). A variety of alcohols and phenol nucleophiles could be added to **1.063** in excellent yield and enantioselectivity, using as low as 0.125-1 mol% of catalyst.[34] This reaction was amenable for use with other nucleophiles, albeit lower enantioselectivity. Among these were aromatic amines and carboxylates, which gave good yields. Malonates were observed to be poor nucleophiles and aliphatic amines were unreactive under these conditions.

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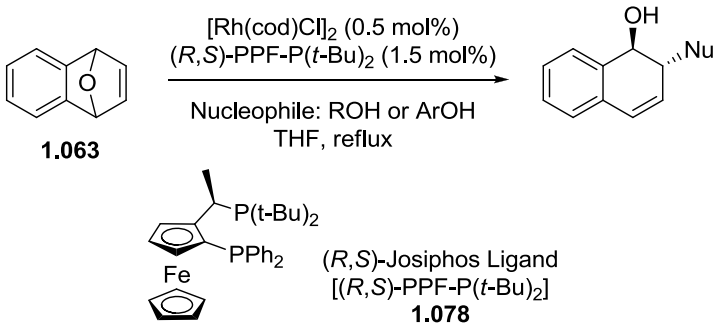
[33] Lautens, M.; Fagnou, K. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5455.

[34] (a) see ref. 31. (b) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677.

Scheme 1-21 Lautens first generation conditions for the Rh(I)-catalyzed oxabicyclic ARO



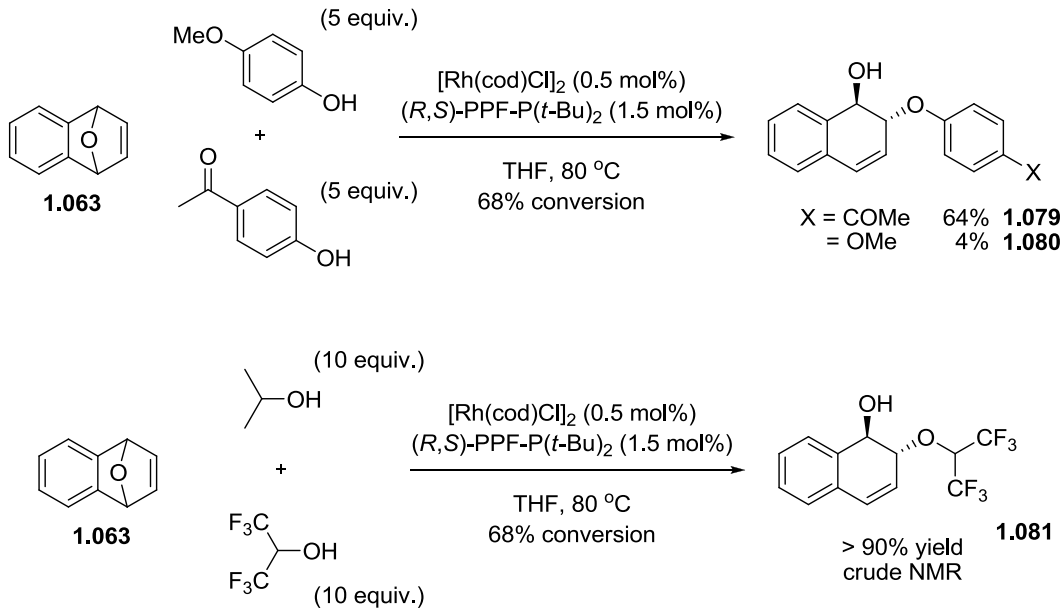
First Generation Conditions

Nucleophile	Result
alcohols and phenols	>90% yield, >90% ee
aliphatic amines	no reaction
aromatic amines	>90% yield, 30-74% ee
malonates	<50% yield, 50% ee
carboxylates	>80% yield, 30-60% ee

A further probe into the reaction mechanism through competition experiments[35] revealed that nucleophiles with lower pK_a values reacted at faster rates (Scheme 1-22). This was established by reacting oxabicycle **1.063** with equal amounts of electron poor 4-acetylphenol, and electron rich 4-metoxyphenol, both in excess. This resulted with a 16:1 selectivity of the products, **1.079** to **1.080**, favouring 4-acetylphenol as the nucleophile. A similar experiment using isopropanol and HFIP resulted with incorporation of HFIP as the sole product **1.081**, despite it being generally considered as a non-nucleophilic reagent. When the alkoxide salt was used as a nucleophile, no product was observed, suggesting that deprotonation of the nucleophile is required for catalyst turnover, and that a labile proton is best suited for this transformation.

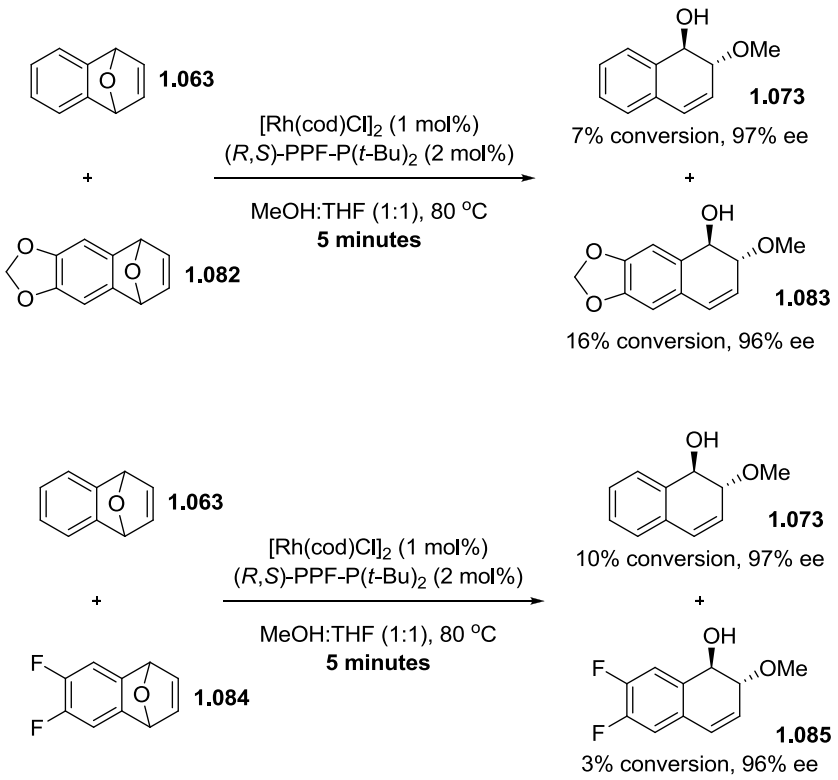
[35] see ref. 32.

Scheme 1-22 Effect of nucleophile pK_a on ring-opening



In addition, electronic effects in substrate were also observed upon modification of oxabicycle **1.063** (Scheme 1-23). Equimolar amounts of electron rich oxabicycle **1.082** and **1.063** were reacted with a methanol nucleophile for 5 minutes to measure product formation. A similar experiment was done using electron poor oxabicycle **1.084**. In the case of the electron rich competition experiment, faster conversion was observed in relation to electron neutral **1.063**. **1.063** fared better than the electron poor substrate. Both set of experiments led to a better understanding of the reaction, which proved to be insightful as a working model is proposed based on this result.

Scheme 1-23 Effect of substrate electronics on ring-opening reaction



The ARO method was then adapted to allow the use of aliphatic amines, which is desirable as many biological interesting structures contain the 2-aminotetralin scaffold,[36] including lysergic acid. It was first discovered that when pyrrolidine was used as a nucleophile, it shut down the reaction by acting as a catalyst poison.[37] Based on the realization that nucleophiles with lower pK_a reacted at faster rates, protic additives were investigated in the ring-opening of **1.063** with pyrrolidine.[38] CSA was found to facilitate the reaction, albeit slowly (Scheme 1-24). When Bu_4NCl was added, it was found to accelerate the reaction. Cooperatively, CSA and Bu_4NCl dramatically increased the reaction rate thereby allowing for the use of aliphatic amines; however, when used individually, either additive lead to unsatisfactory results. At that time, bidentate dppf was believed to have comparable reactivity to the Joisphos ligand **1.078**.

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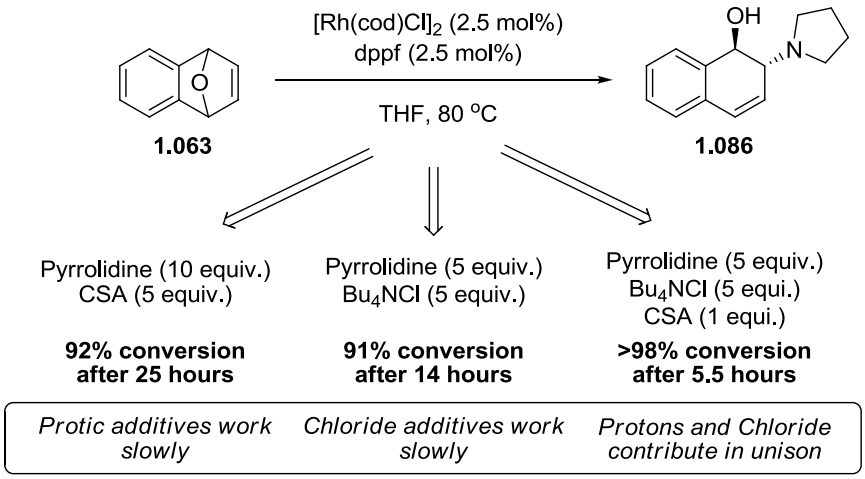
[36] (a) Koe, B.; Weissman, A.; Welch, W.; Browne, R. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 686. (b) Szmuszkovicz, J., et al. *J. Med. Chem.* **1991**, *34*, 1891. (c) Zhang, Y.; Tropsha, A.; McPhail, A.; Lee, K. *J. Med. Chem.* **1994**, *37*, 1460. (d) Necas, M.; Dostal, J.; Kejnovska, I.; Vorlickova, M.; Slavik, J. *J. Mol. Struct.* **2005**, *734*, 1.

[37] Lautens, M.; Fagnou, K.; Yang, D.Q. *J. Am. Chem. Soc.* **2003**, *125*, 14884.

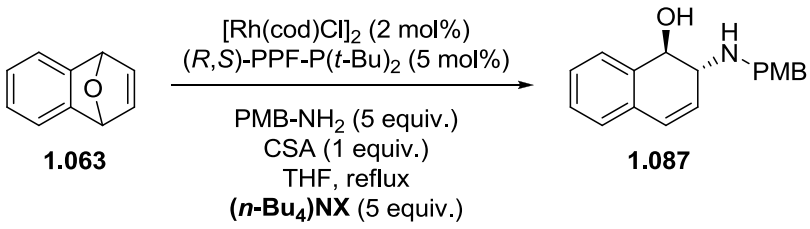
[38] see ref. 36.

Scheme 1-24 Solution to circumvent catalyst poisoning by amines through the use of protic and halide additives



The nature of the halide additive also affected the enantioselectivity (Scheme 1-25).[39] Ring opening of **1.063** using PMB-NH_2, using ligand **1.078** and excess Bu_4NX additive showed increasing enantioselectivity by this trend: Cl < Br < I. When a halide exchange protocol was employed using a AgOTf additive, to form cationic Rh, the *ee* was improved.

Scheme 1-25 Effect of halide additives on the enantioselectivity of the ring-opening reaction using an aliphatic amine



Halide	Result
Cl	52% yield, 29% ee
Br	67% yield, 42% ee
I	72% yield, 72% ee
I*	71% yield, 81% ee

* Additive: AgOTf (5 mol%)

Further modification of the conditions established the improved 2nd generation ARO conditions, which was diverse in the range of nucleophiles and provided a robust reaction with high yields and enantioselectivity (Scheme 1-26). CSA was replaced with NH_4I as the protic

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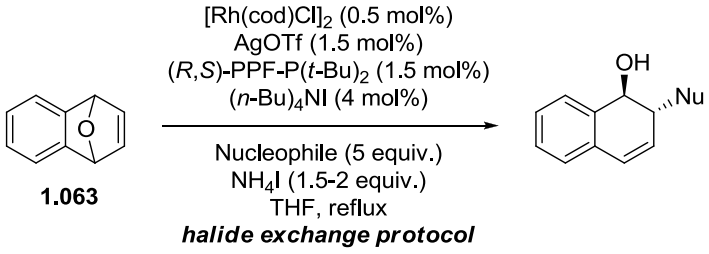
[39] (a) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170. (b) Fagnou, K.; Lautens, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 26.

additive, and was used in lower excess than before. The Rh-I catalyst formed in situ proved to be significantly more active than the first generation conditions, giving high yields and enantioselectivities for all nucleophilic classes, including those that reacted poorly. The counterion is believed to coordinate to the metal centre during the enantiodiscriminating step, oxidative insertion to bridging C-O bond, thereby affecting the rhodium-phosphorus bond length in the chiral ligand-metal complex. The resulting *trans* effect would shift the chiral motif closer to the site of the reaction.

Scheme 1-26 Improved second generation ARO conditions using iodide as a counterion



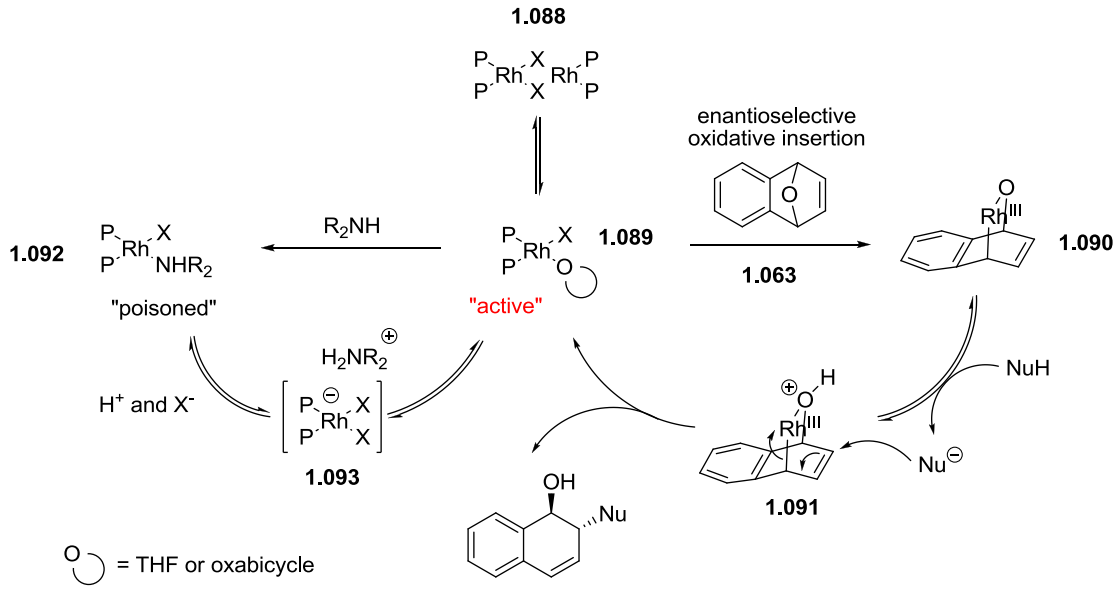
Second Generation Conditions

Nucleophile	Result
alcohols and phenols	>90% yield, >90% ee
aliphatic amines	>80% yield, >90% ee
aromatic amines	>90% yield, >90% ee
malonates	>90% yield, >90% ee
carboxylates	>70% yield, >90% ee

A working mechanistic model has been proposed (Scheme 1-27).[40] The dimeric bridged Rh(I) pre-catalyst **1.088** dissociates to form the active catalyst **1.089**, a monomeric Rh(I) species. An enantioselective oxidative insertion into one of the bridging C-O bonds of **1.063** gives rise to a Rh(III) intermediate, **1.090**. Protonation of this intermediate provides activated complex **1.091**, which is then attacked by a nucleophile in an S_N2' fashion to afford the product and regenerate active **1.089**. **1.089** is prone to be in a poisoned state **1.092** upon sequestering with an amine nucleophile. Protic and halide additives work to protonate the metal-bound nitrogen and displace the ammonium salt to the form the dihalide complex **1.093**, thus reversing the catalyst inhibition to allow for productive catalytic turnover.

[40] (a) See ref. 32 and 36. (b) Fleming, M.; Lautens, M.: Carbon-Heteroatom Bond Formation by Rh(I)-Catalyzed Ring-Opening Reactions (Chapter) "Catalyzed Carbon-Heteroatom Bond Formation" A. K. Yudin (Ed.): John Wiley & Sons Ltd.: Chichester, **2010**.

Scheme 1-27 Working mechanistic model to account for the effect of protic and halide additives in the Rh(I)-catalyzed ring opening



Following this report, many others have extended the ARO methodology to other nucleophiles, including thiols, boronic acids, and more recently, water.[41] This led to the realization of an interesting reaction pathway as it relates to using boronic acids as a nucleophile, which furnishes ARO products in the opposite stereochemistry as heteroatom nucleophiles, despite using the same catalyst system. This topic is outside the scope of this discussion, and additional material can be found in these supporting documents.[42]

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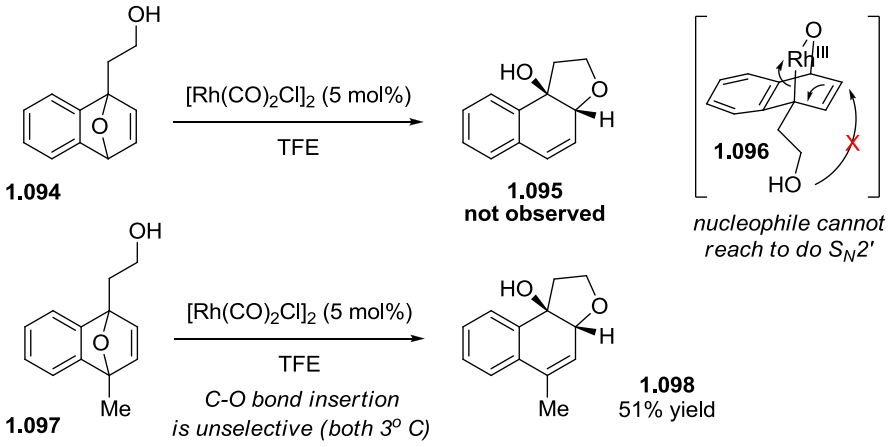
[41] (a) thiols: Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194. (b) aryl-boronic acids: Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311; Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390; Dockendorff, C., *Ph.D. Thesis*, University of Toronto, **2006**; Fagnou, K., *Ph.D. Thesis*, University of Toronto, **2002**. (c) ring-opening/dimerization: Nishimura, T.; Kawamoto, T.; Sasaki, K.; Tsurumaki, E.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 1492; Allen, A.; Le Marquand, P.; Burton, R.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2007**, *72*, 7849. (d) terminal alkynes to azabenzonorbornadienes: Nishimura, T.; Tsurumaki, E.; Kawamoto, T.; Guo, X.; Hayashi, T. *Org. Lett.* **2008**, *10*, 4057. (e) Water: Tsui, G.C.; Lautens, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 5400.

[42] Webster, R., *Ph.D. Thesis*, University of Toronto, **2011**.

1.2.3 Rhodium Catalyzed Desymmetrization of *meso* Bridgehead-Substituted Oxabicyclic Alkenes

The seminal experiments that led to the study of desymmetrization reactions of *meso* bridgehead substituted oxabicycles were first investigated by Fagnou (Scheme 1-28).[43] Racemic oxabicycle **1.094** was prepared possessing a nucleophilic side chain at the bridgehead position to see if intramolecular ring-opening could occur. Subjecting **1.094** under $[Rh(CO)_2Cl]_2$ catalytic conditions in TFE did not furnish **1.095**. This was presumed to be because the catalyst would preferentially insert into the proximal C-O bond at the more substituted position thereby activating the end of the alkene distal to the nucleophilic side chain, preventing S_N2' attack (**1.096**). To test this hypothesis, oxabicycle **1.097** was synthesized and reacted under identical conditions, affording the ring-opened fused tricylic compound **1.098** in 51% yield. In oxabicycle **1.097**, the Rh(I) insertion into the bridgehead C-O bond would have been indiscriminant as both bridgehead carbon atoms are electronically and sterically similar. Therefore, it would be expected that only 50% of the desired distal C-O bond would be inserted to allow for cyclization to occur, leaving with the remaining half to decompose. This hypothesis is reflected in the observed yield.

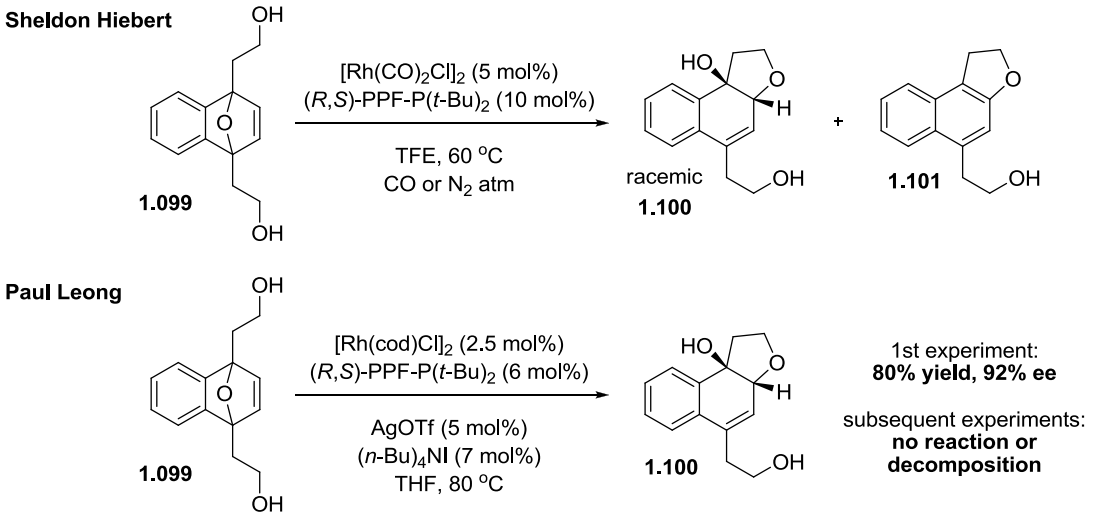
Scheme 1-28 Effect of bridgehead substitution on the intramolecular ring-opening of benzofused oxabicyclic alkenes



[43] Fagnou, K., *Ph.D. Thesis*, University of Toronto, **2002**.

This result prompted the desymmetrization of *meso* bridgehead substituted oxabicycle **1.099** bearing identical side chains. Sheldon Hiebert was the first doctoral student to examine this transformation (Scheme 1-29).[44] It was found that using $[Rh(CO)_2Cl]_2$ with ligand **1.078** in TFE produced cyclized product **1.100** as a racemic mixture, accompanied by unwanted aromatized **1.101**. Paul Leong revisited this reaction and used $[Rh(cod)Cl]_2$ instead, employing the halide exchange protocol,[45] which furnished the cyclized product **1.100** in 80% yield and 92% ee.[46] However, despite all efforts, the experiment was not reproducible and the project was temporarily abandoned, leaving the cause of the initial result to being unknown.

Scheme 1-29 Initial studies of the intramolecular ARO of symmetrical substrates



The project was later revisited by Robert Webster. A number of conditions[47] to screen the intramolecular ring-opening / cyclization of **1.099** were attempted, but were unsuccessful. The $[Rh(cod)Cl]_2$/Josiphos catalyst system was found to be ineffective with varying solvents, temperature, protic additives, even the use of a Rh-I species. In addition, palladium and copper catalysts were examined but were not successful. Webster was moderately successful when **1.099**was subjected to methanolysis conditions, analogous to Hogeveen and Middelkoop to

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[44] Hiebert, S., *Ph.D. Thesis*, University of Toronto, **2003**.

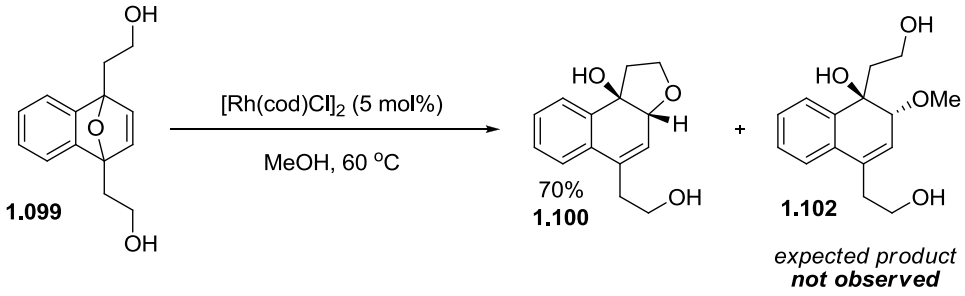
[45] see 1.3.2 – 2nd Generation Ring Opening Conditions

[46] Leong, P., *Ph.D. Thesis*, University of Toronto, **2007**.

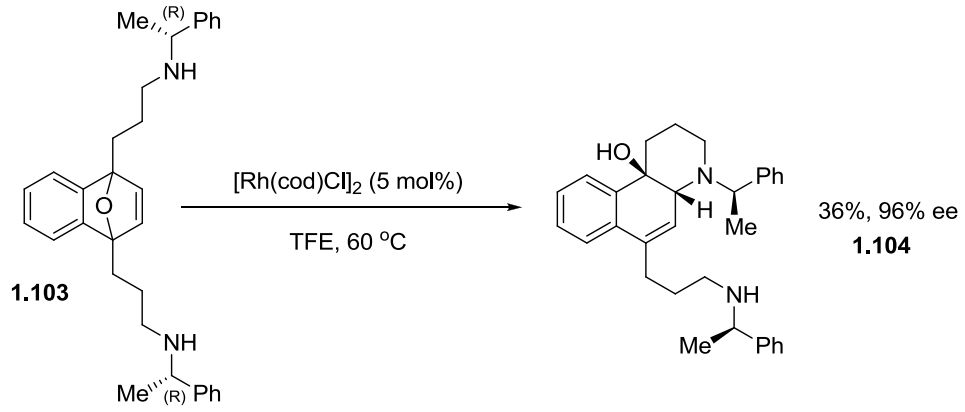
[47] Webster, R., *Ph.D. Thesis*, University of Toronto, **2011**.

furnish the desired tryicyclic product **1.100** in 70% yield as a racemate (Scheme 1-30). He did not detect any amount of expected **1.102**, despite the use of methanol as solvent. It became apparent that the addition of a ligand inhibited the intramolecular reaction, and the use of chiral ligands in the reaction were not possible, unlike the intermolecular reactions. This led to the investigation of a ligand-free diastereoselective cyclization using a chiral auxillary installed on 'pseudo-*meso*' oxabicycle **1.103** to furnish tricyclic product **1.104** (Scheme 1-31).

Scheme 1-30 Webster's attempted methanolysis of meso-oxabicycles



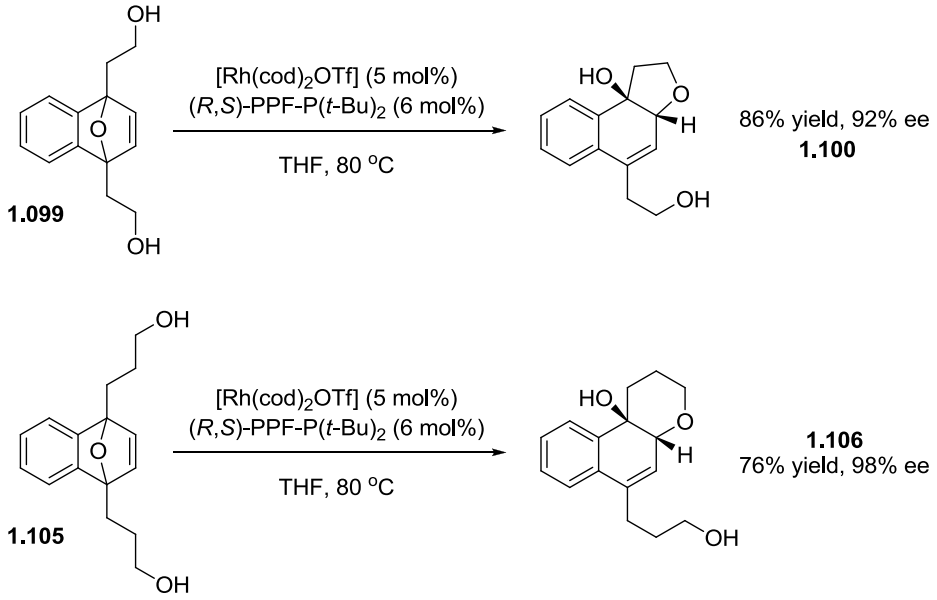
Scheme 1-31 Adapted ring-opening conditions using a pseudo-meso oxabicycle



Upon further screening oxabicycle **1.099** was successfully desymmetrized by using the more reactive catioinic Rh catalysts possessing weakly coordinating, or non-coordinating counterions such as ^{-}OTf, $^{-}BF_4$, and $^{-}BArF_4$ (Scheme 1-32). These catalysts were generally found to be too reactive with oxabicycles containing no bridgehead substitution, often resulting in decomposition and byproduct formation. However, knowing that ligand **1.078** poisoned $[Rh(cod)Cl]_2$ catalyst, it was believed that a more electrophilic catalyst was required to facilitate the reaction. The most effective catalyst was $[Rh(cod)_2OTf]$, which gave **1.100** in excellent yield

and enantioselectivity without the need for additives. This reaction was applied to homologous oxabicycle **1.105**, to furnish six-membered **1.106**. Both experiments were consistently reproduced. Furthermore, the addition of a halide additive, TBAI or TBACl, shut down reactivity, confirming the catalyst's counterion has a profound effect on the reactivity.

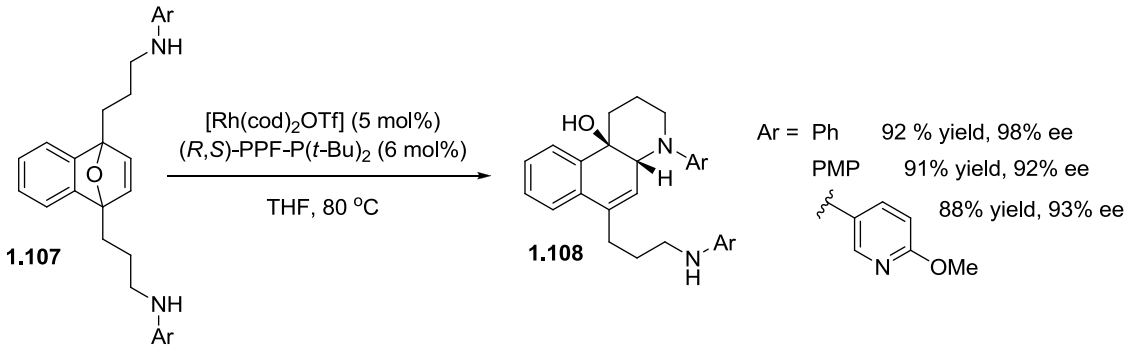
Scheme 1-32 Efficient and successful enantioselective desymmetrization using cationic Rh



The work of Webster was extended to nitrogen bearing oxabicyclic nucleophiles **1.107** (Scheme 1-33). Anilines were found to be excellent substrates for the intramolecular ring-opening reaction. Beyond this, not many functional groups have been investigated and room exists for the expansion of the scope to include aliphatic nitrogen, sulphur and carbon nucleophiles. Currently, Shabnam Yazdi is investigating the Rh-Catalyzed arylative/alkylative ARO of *meso* bridgehead substituted oxabicyclic alkenes. More information on seminal reports can be found in this reference[48] along with Shabnam's contributions as they appear in the literature.

[48] see ref. 46.

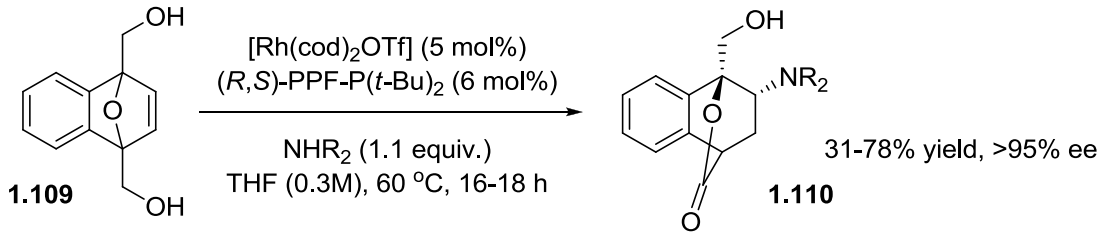
Scheme 1-33 Enantioselective desymmetrization of meso-oxabicycles using bis-anilines



The structural motifs possessed by **1.108** (Scheme 1-33) bears the ACD fused tricyclic ring system of lysergic acid in the correct absolute stereochemistry. However, a synthetic strategy to make **1.015** from these cyclic aminotetralines would prove to be unnecessarily lengthy, given the overly large bridgehead substitution opposite to the cyclized product, which contain too many carbons to form the indole. Nonetheless, this work sets the precedent for an intermolecular strategy towards the synthesis of **1.015**.

The most recent contribution in the area of Rh-catalysed desymmetrization of *meso* substituted oxabicycles is that of Alisatir Boyer's work in 2011 (Scheme 1-34).[49] A novel domino asymmetric transformation was developed. Using *meso*-substituted **1.109** under [Rh(cod)$_2$OTf]/(*R*,*S*)-Josiphos catalysis with various amine nucleophiles furnished bicyclo-[2.2.2]-lactones **1.110** in good yield and excellent enantioselectivity.

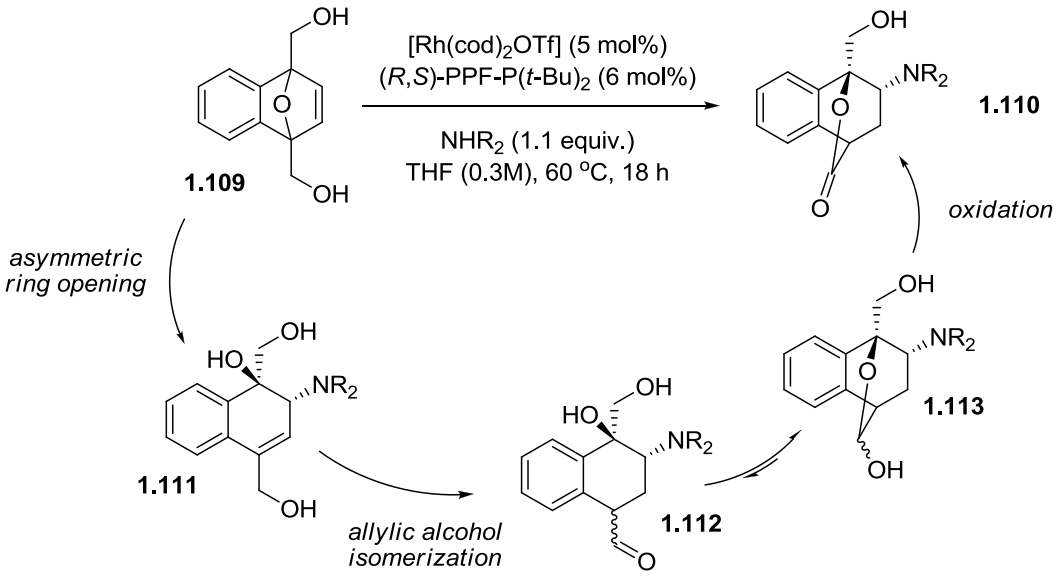
Scheme 1-34 Boyer's desymmetrization of bridgehead substituted oxabicycles to form enantiopure lactones



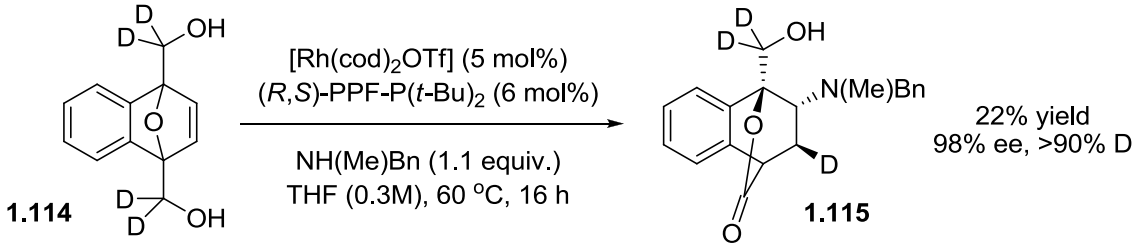
[49] Boyer, A.; Lautens, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7346.

The formation of highly complex enantiopure 2-aminotetralines has the potential to be a useful synthon towards the synthesis of lysergic acid as the induced absolute stereochemistry matches that of the natural product. A closer investigation into the reaction mechanism suggests that this process proceeds by a rhodium-catalyzed ARO first, forming ring-opened product **1.111** (Scheme 1-35). This is followed by isomerization of the allylic alcohol to aldehyde **1.112**, which upon formation of hemiacetal **1.113**, oxidizes to form the lactone product **1.110**. The reason for this proposal is that **1.109** was found to rapidly form **1.111** first during optimization. When **1.111** was subjected to the same conditions, lactonized product **1.110** formed over time. Deuterium labeled substrate **1.114** reacted to give the product **1.115**, which is consistent with the proposed mechanism (Scheme 1-36). This reaction is very interesting given that rhodium plays three distinct roles in the reaction: ARO, allylic alcohol isomerization, and oxidation. A more detailed mechanistic investigation will be necessary to identify what is happening at the metal center throughout these transformations to account for oxidation and reduction, as no other additives to justify this are used. In this segment, progress towards the total synthesis of **1.015** using ARO as an alternative to previously established routes is described.

Scheme 1-35 Proposed mechanism for the lactonization reaction accounting for the ARO of various amines



Scheme 1-36 Deuterium labeling studies of the asymmetric lactonization

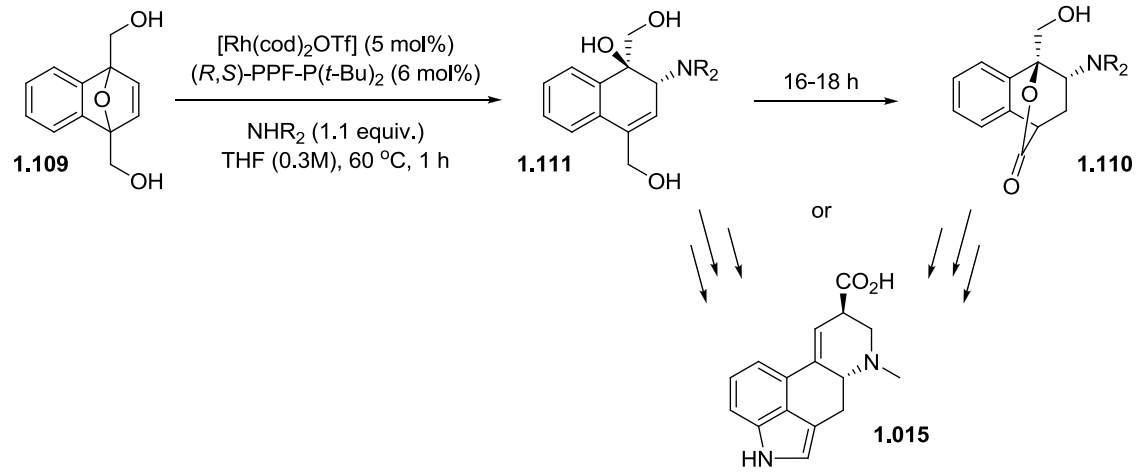


1.3 Results and Discussions

1.3.1 C-H Amination Strategy

Webster's set the stage for Boyer to develop the intermolecular ARO of *meso*-bridgehead substituted oxabicycles using an amine nucleophile. With a reliable method to prepare either the ring-opened **1.111** or bicyclic lactone **1.110**, the synthesis towards the **1.015** was pursued using either intermediate (Scheme 1-37).

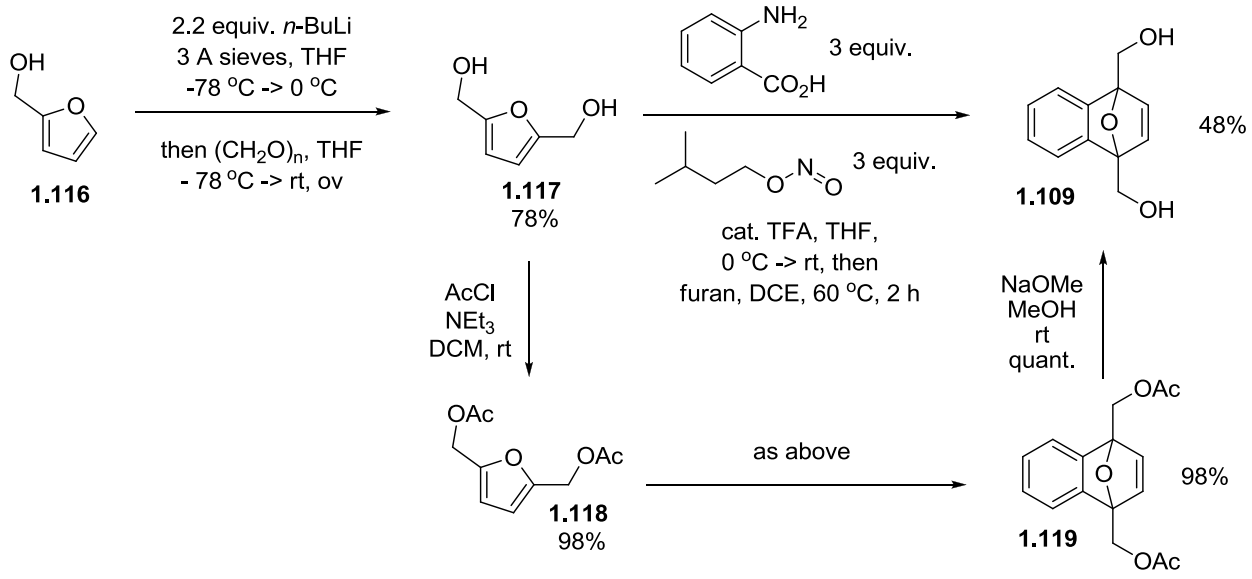
Scheme 1-37 Proposed route to **1.015** using either ring-opened or lactonized products



The requisite oxabicycle **1.109** was accessed by an aryne DA reaction of diol **1.117** and benzyne, generated from anthranilic acid (Scheme 1-38). Diol **1.117** was prepared from furfuryl alcohol **1.116** by treatment with 2.2 equivalents of *n*-BuLi to generate the 5-lithiated species and quenched with paraformaldehyde in 78% yield. Anthranilic acid was treated with isoamyl nitrite and a catalytic amount of TFA to give the anthranilic acid diazonium salt, which precipitated in

solution. This salt was then slurried into a solution of the furan, and upon heating to 60 °C formed **1.109** directly in 48% yield, with concomitant release of CO_2 and N_2 as benzyne was generated. Treatment of the diazonium intermediate with bis-acetoxy protected furan **1.118** allowed for higher throughput of **1.109** from **1.119** given the higher yields obtained. As a result, the introduction of the protection group and subsequent removal improved the overall yield of **1.109** substantially.

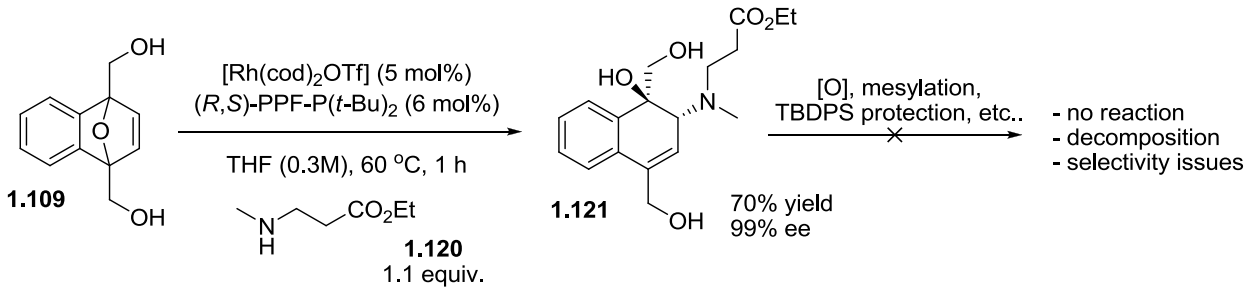
Scheme 1-38 Synthesis of meso-benzofused oxabicyclic alkene **1.109**



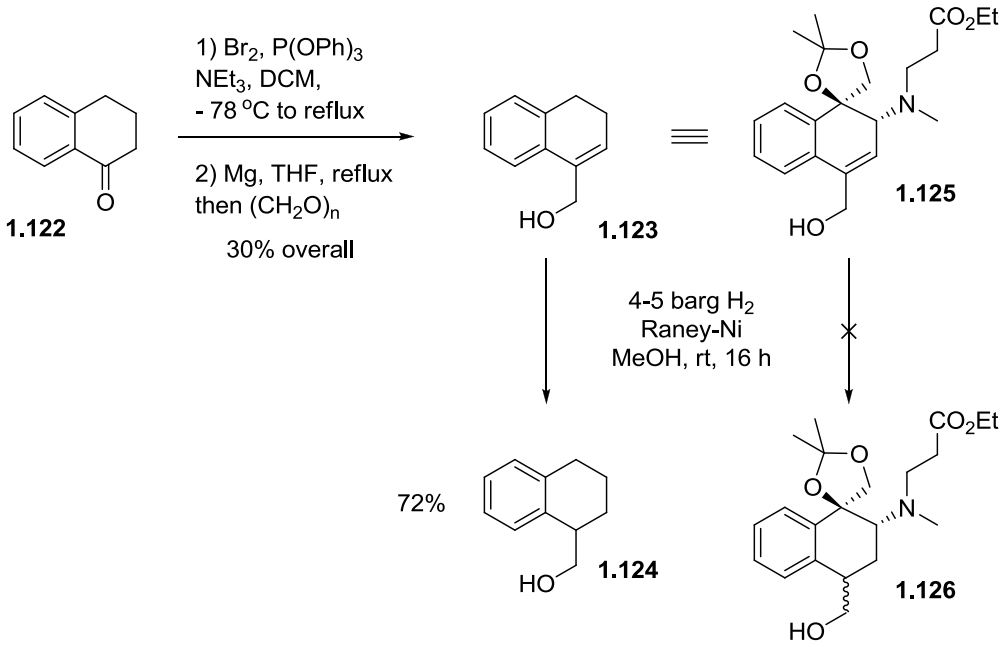
Initial efforts studied the use ring-opened triol **1.121** as opposed to **1.110** given the shorter reaction time to form **1.121** (Scheme 1-39). **1.121** was isolated in 70% yield using secondary alkyl amine **1.120**, bearing the necessary functionality to annulate the **D** ring as in past syntheses. Attempts to manipulate **1.121** by differentiating between hydroxyl groups based on reactivity (primary allylic vs. primary vs. tertiary) showed that these substrates were prone to decomposition or that there was comparable reactivity between functional groups, causing selectivity issues. Boyer proposed decomposition could be circumvented by reduction of the double bond. The hydrogenation of the tri-substituted double bond was not trivial, and all efforts

failed despite finding RaNi to operate on model substrate **1.123** derived from **1.122** (Scheme 1-40). Extensive experimental details can be found in this report.[50]

Scheme 1-39 Attempted manipulations of ring-opened products



Scheme 1-40 Model study of the hydrogenation onto the trisubstituted double bond

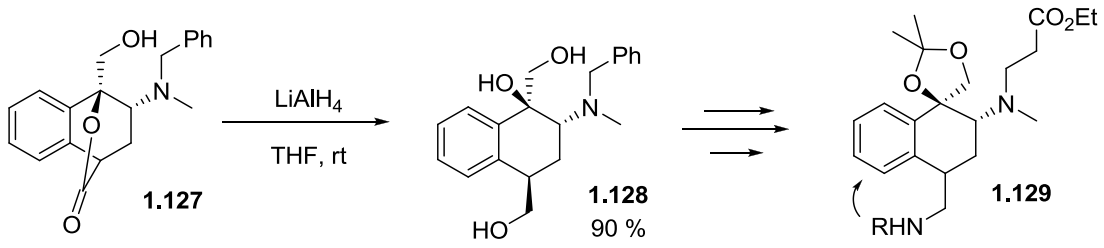


Although attempts to use ring-opened triol **1.121** were cumbersome, the use of lactone product **1.110** provided a solution. Upon reduction of **1.110** with $LiAlH_4$, triol **1.128** was formed in excellent yield and stereocontrol, which would not be otherwise guaranteed with hydrogenation (Scheme 1-41). Attention was turned to finding a method to prepare the **B** ring of

[50] Boyer, A., *Postdoc. Report*, University of Toronto, **2011**.

lysergic acid by a C-H amination of **1.129**, as this step would be pivotal in the preparation of the natural product given its novelty. The construction of the **D** ring can be left for later as methods to its preparation are already established from previous syntheses.[51]

Scheme 1-41 Alternate route to forming saturated ring-opened products towards C-H amination



The C-H amination of reduced lactonized product **1.128** was probed. A summary of this investigation is briefly described, and more details can be found in Boyer's report. The preparation of various indoles and indolines recently reported in the literature (Scheme 1-42) were analogously tried onto the model substrate **1.123** to test its potential as a viable method. Among them was Moody's[52] nitrene based C-H amination to form a tricyclic indole with high homology to **1.015**. This transformation occurs by the C-H insertion of a nitrene, generated by thermal decomposition of a vinyl azide. More recently, Driver[53] and Narasaka[54] have used Rh(II) catalysts as an alternative to allow this transformation to be done at lower temperatures. When applying these methods to the corresponding model allylic azide **1.124** (Scheme 1-43), as opposed to a vinyl azide as it would have required several steps to make, the indole could not be formed. It is likely that an sp^2-azide was necessary for the reaction, causing the formation of the nitrene species for **1.124** to be slow. This finding warrants a vinyl azide to be tested before ruling this strategy out. The azirine could not be accessed from **1.123** despite Boyer's efforts and Narasaka's method was not tried.

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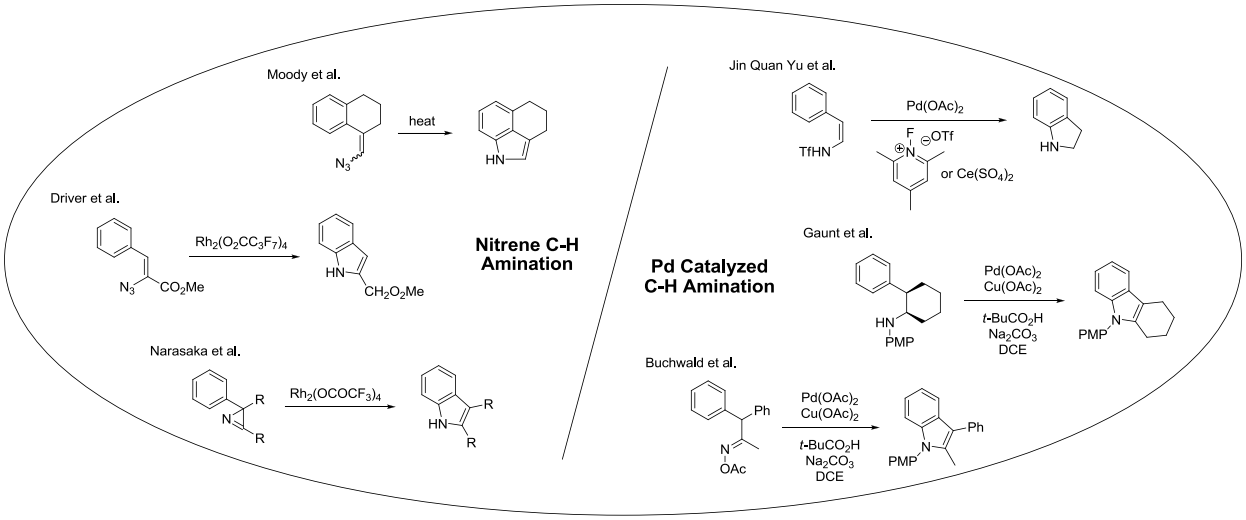
[51] see Section 1.2

[52] Moody, C.J.; Beck, A.L.; Coates, W.J.; *Tetrahedron Lett.* **1989**, *30*, 4017; *J. Chem. Soc. Perkin 1* **1990**, 689.

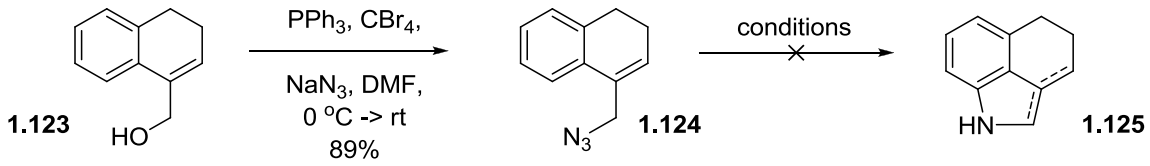
[53] Stokes, B.J.; Dong, H.; Leslie, B.E.; Pumphrey, A.L.; Driver, T.G.; *J. Am. Chem. Soc.* **2007**, *129*, 7500.

[54] Narasaka, K., et al. *Chem. Lett.* **2007**, 52.

Scheme 1-42 Various methods proposed to C-H aminate substituted tetralones



Scheme 1-43 Model study of the cyclization using an allylic nitrene



Attention was then turned to use of palladium-catalyzed C-H amination (Scheme 1-42). The work Yu,[55] Gaunt,[56] and Buchwald[57] sets the precedent for this strategy. Yu reports a direct synthesis of indolines using electron poor triflamides to weakly coordinate and direct ortho-palladation. Additional oxidant serves to oxidize the intermediate palladium-(II) complex to promote reductive elimination. Gaunt developed the use of an electron rich N-PMP to form indolines in their method using Cu(II) as the oxidant, forming some indole in the process. Buchwald developed the use of an *O*-acetyl oxime to carry out this process to form indoles, with the substrate acting as the oxidant itself.

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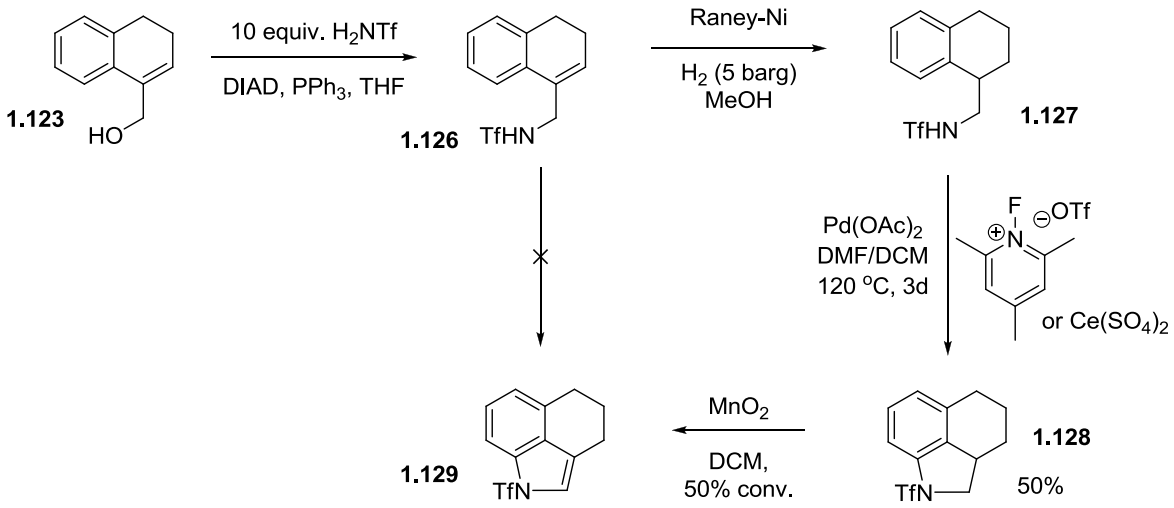
[55] Mei, T-S.; Wang, X.; Yu, J-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806; Engle, K.M.; Mei, T-S.; Wang, X.; Yu, J-Q. *Angew. Chem. Int. Ed.* **2011**, *50*, 1478.

[56] Haffemayer, B.; Gulias, M.; Gaunt, M.J. *Chem. Sci.* **2011**, *2*, 312.

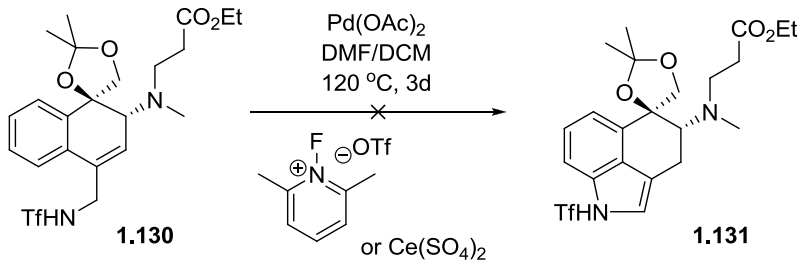
[57] Tan, Y.; Hartwig, J.F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

Investigation of the triflamide function using the model substrate **1.127**, prepared from **1.123** by a Mitsunobu reaction and subsequent hydrogenation, proved successful in preparing fused tricycle **1.128** (Scheme 1-44). It was possible to oxidize **1.128** to form the fused indole **1.129**. **1.129** could not otherwise be formed directly from **1.126** as previous observations showed the tendency for these allylic substrates to decompose. No reaction was observed upon application of this method to ring-opened oxabicyclic intermediate **1.130** (Scheme 1-45). As there was no decomposition, it was not likely the allylic double bond had a role in the failure of this reaction. Rather, the presence of the tertiary amine poisoned the catalyst given it is more apt to coordinate than the weakly coordinating triflamide. Yu had already highlighted that triflate was the only protecting group tolerated by the reaction. For this strategy to work on **1.130**, the other amine had to be protected with a triflate, making the synthesis unnecessarily complex.

Scheme 1-44 Model studies of the ring-closing reaction using triflamides

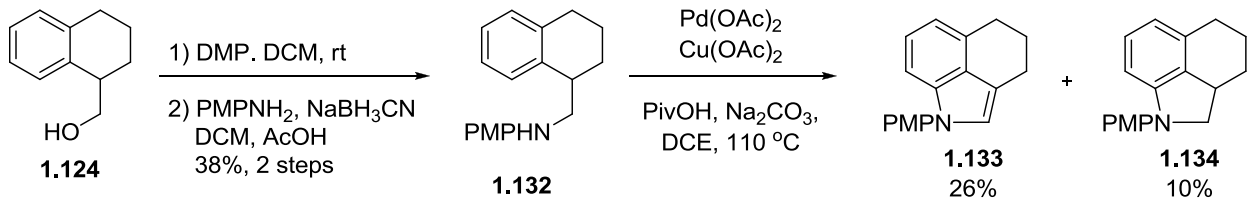


Scheme 1-45 Unsuccessful Pd-catalyzed cyclization using a triflamide onto **1.130**

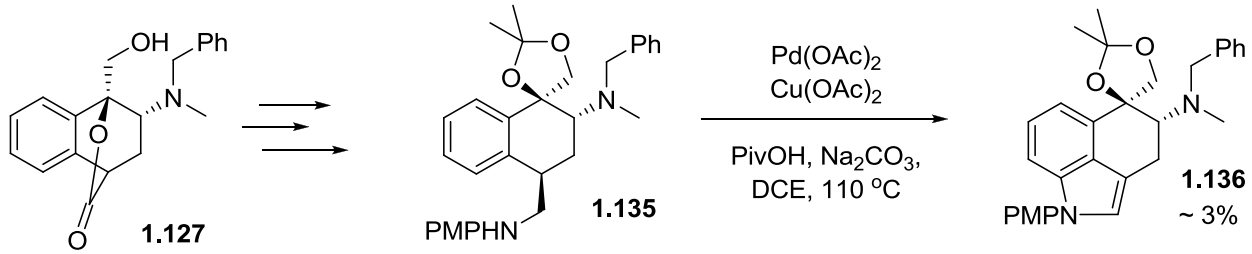


A model study of Buchwald's method did not prove fruitful and was not pursued further. Attention was turned to Gaunt's protocol, which showed some promise in the model studies (Scheme 1-46). Although a distribution of products was formed, the desired indole **1.133** was isolated in 26%, along with indoline **1.134** in 10%. Application of this method to N-PMP intermediate **1.135**, generated desired indole **1.136**, albeit in minute quantities (Scheme 1-47). Optimization of this reaction may be a promising pursuit towards the natural product.

Scheme 1-46 Cyclization model study using an N-PMP group



Scheme 1-47 Application of Pd-catalyzed cyclization of an N-PMP group using **1.135**

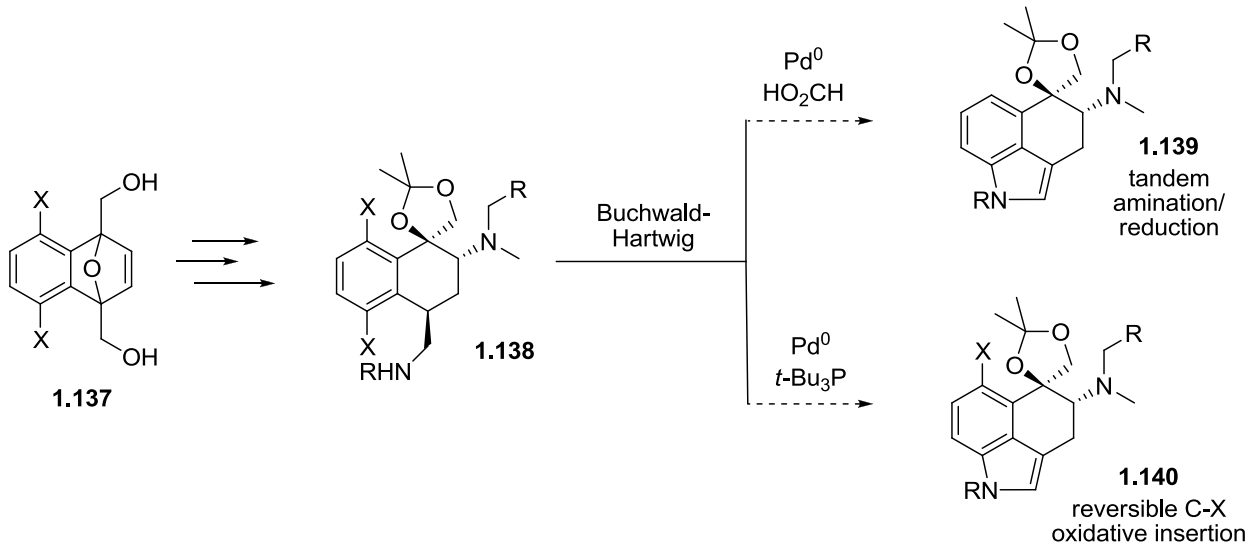


1.3.2 Alternative Indole Formation via Buchwald-Hartwig Amination

An alternative route to the one investigated to furnish the indole was considered (Scheme 1-48). By installing two halides symmetrically on the aromatic backbone of oxabicycle **1.137**, it was proposed that a Buchwald-Hartwig amination could provide a solution to constructing the indole. However, the presence of a second halide on substrate **1.138** may lead to catalyst/product decomposition. This could be overcome by the addition of a reducing agent, formic acid, to promote the regeneration of the catalyst by a tandem reduction of the second halide to give

1.139. A bulky phosphine ligand may also serve to regenerate the active palladium catalyst by reductive elimination of the C-X bond to preserve the halide[58] in the product **1.140**.

Scheme 1-48 Proposed amination route using a Buchwald-Hartwig coupling



The dihalo-substituted anthranilic acid is not commercially available and had to be synthesized using a 3-step literature procedure.[59] Starting from dihalo compound **1.141**, the amine is first functionalized with an acyl-aldoxime **1.142**. The crude material is then subjected to a Friedel-Crafts ring closing to prepare the isatin, followed by oxidative base hydrolysis to liberate **1.143** in 44 % and **1.144** in 59 % yield for the dibromo- and dichloroanthranilic acid, respectively. The dihalo-oxabicyclic starting material was then synthesized by a one pot, *in situ* aryne DA reaction of **1.118** with the corresponding dibromo- **1.145** and dichloroanthranilic acid **1.146** in 90% and 80% yield, respectively (Scheme 1-49). Oxabicycle **1.146** was readily converted to the free unprotected diol under methanolysis conditions quantitatively.

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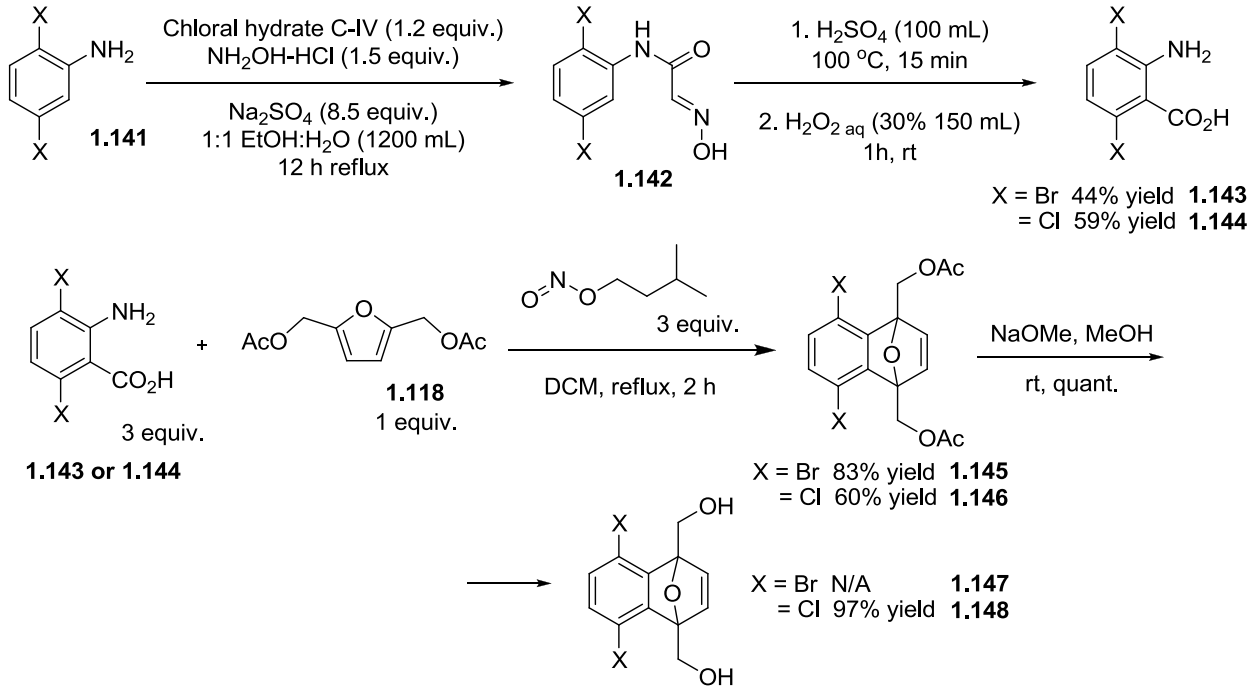
[58] Newman, S.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416.

[59] Miljanić, O.Š.; Vollhardt, K.P.C.; Whitener, G.D. *Synlett* **2003**, 29; Lisowski, V.; Robba, M.; Rault, S. *J. Org. Chem.* **2000**, *65*, 4193.

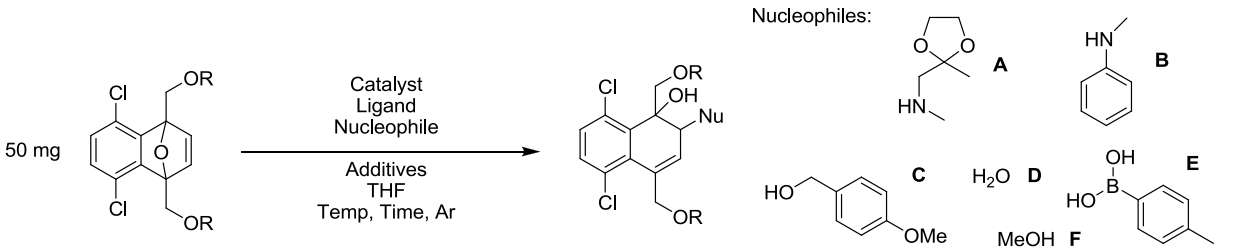
Scheme 1-49 Synthesis of meso-dihalosubstituted oxabicyclic alkenes **1.147** & **1.148**



Each substrate was treated to ring-opening conditions as to evaluate its reactivity. Preliminary trials had established that these oxabicycles could not open, but time did not permit a full investigative study. A deeper study was warranted and the dihalooxabicycles were subjected to numerous conditions developed in the Lautens group to evaluate its reactivity further (Table 1-1). Despite using optimal conditions on varying heteroatom, carbon, and more recently water as nucleophiles, none of the conditions[60] served to effect any transformation and the substrates remained intact.

[60] see Sections 1.3.2 and 1.3.3.

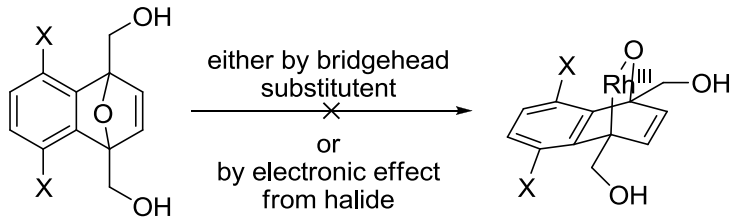
Table 1-1 Screen of conditions to effect ring-opening reaction onto dichloro-oxabicyclic alkenes



Entry	R	Catalyst (mol %)	Ligand (mol %)	Nucleophile (equiv.)	Comments (equiv.)	T	Time	Result
1	OAc	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	No Additives; 0.1 M THF	60 °C	1 h	NR
2	OAc	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	No Additives; 0.3 M THF	60 °C	16 h	NR
3	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	No Additives; 0.1 M THF	60 °C	1 h	NR
4	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	No Additives; 0.3 M THF	60 °C	16 h	NR
5	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	0.1 M THF Bu_4NI (5), CSA (1)	60 °C	2 h	NR
6	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	0.1 M THF Bu_4NI (5), CSA (1)	60 °C	16h	NR
7	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**B** (1.1)	0.1 M THF Bu_4NI (5), CSA (1)	60 °C	2 h	NR
8	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**B** (1.1)	0.1 M THF Bu_4NI (5), CSA (1)	60 °C	16 h	NR
9	OH	$[Rh(cod)Cl]_2$ (2.5)	DPPF (5)	**A** (1.1)	0.1 M THF Bu_4NI (5), CSA (1)	60 °C	2 h	NR
10	OH	$[Rh(cod)Cl]_2$ (2.5)	DPPF (5)	**A** (1.1)	0.1 M THF Bu_4NI (5), CSA (1)	60 °C	16 h	NR
11	OH	$[Rh(cod)Cl]_2$ (2.5)	DPPF (5)	**B** (1.1)	0.1 M THF Bu_4NI (5), CSA (1)	60 °C	2 h	NR
12	OH	$[Rh(cod)Cl]_2$ (2.5)	DPPF (5)	**B** (1.1)	0.1 M THF Bu_4NI (5), CSA (1)	60 °C	16 h	NR
13	OH	$[Rh(cod)OH]_2$ (2.5)	(*R*,*S*) JosiPhos (5)	**A** (1.1)	No Additives, 0.1 M THF	80 °C	16 h	NR
14	OH	$[Rh(CO)_2Cl]_2$ (2.5)	(*R*,*S*) JosiPhos (5)	**A** (1.1)	No Additives, 0.1 M THF	80 °C	16 h	NR
15	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	No Additives; 0.1 M HFIP	80 °C	16 h	NR
16	OAc	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	No Additives; 0.1 M HFIP	80 °C	16 h	NR
17	OH	$[RhI(PPF\text{-}P^tBu_2]$ (2.5)	---	**A** (5.0)	0.1 M THF, NH_4I (2.5)	80 °C	16 h	NR
18	OH	$[RhI(PPF\text{-}P^tBu_2]$ (2.5)	---	**B** (5.0)	0.1 M THF, NH_4I (2.5)	80 °C	16 h	NR
19	OH	$[Rh(cod)Cl]_2$ (2.5)	(*S*,*R*) JosiPhos (5)	**C** (5.0)	No Additives, 0.1 M THF	80 °C	16 h	NR
20	OAc	$[Rh(cod)Cl]_2$ (2.5)	(*S*,*R*) JosiPhos (5)	**C** (5.0)	No Additives, 0.1 M THF	80 °C	16 h	NR
21	OH	$[Rh(cod)Cl]_2$ (5)	(*S*,*R*) JosiPhos (10)	**D** (60)	No Additives, 0.2 M THF	25 °C	16 h	NR
22	OH	$[Rh(cod)Cl]_2$ (5)	(*S*,*R*) JosiPhos (10)	**D** (60)	No Additives, 0.2 M THF	80 °C	16 h	NR
23	OAc	$[Rh(cod)Cl]_2$ (5)	(*S*,*R*) JosiPhos (10)	**D** (60)	No Additives, 0.2 M THF	25 °C	16 h	NR
24	OAc	$[Rh(cod)Cl]_2$ (5)	(*S*,*R*) JosiPhos (10)	**D** (60)	No Additives, 0.2 M THF	80 °C	16 h	NR
25	OH	$Pd(MeCN)_2Cl_2$ (6)	DPPP (6)	**E** (1.2)	0.1 M THF, Cs_2CO_3 (0.5) 1:100 H_2O:THF	80 °C	16 h	NR
26	OH	$Pd(MeCN)_2Cl_2$ (6)	DPPP (6)	**E** (1.2)	0.1 M MeOH, Cs_2CO_3 (0.5) 1:100 H_2O:MeOH	80 °C	16 h	NR
27	OH	$[Rh(cod)Cl]_2$ (5)	(*S*,*R*) JosiPhos (10)	**F** (30)	No Additives, 0.2 M THF	80 °C	16 h	NR
28	OAc	$[Rh(cod)Cl]_2$ (5)	(*S*,*R*) JosiPhos (10)	**F** (30)	No Additives, 0.2 M THF	80 °C	16 h	NR

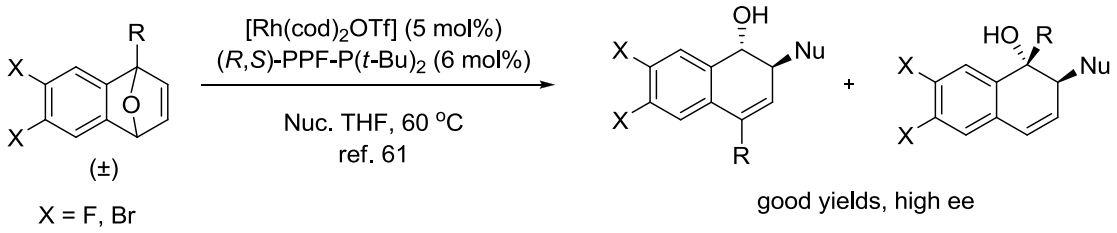
Two theories are presented concerning the unreactive nature of the substrate (Scheme 1-50). To date, no bridgehead substituted oxabicycle containing a halide substituent on either of the two aromatic positions adjacent to the fused bicycle has ever been opened, leaving to suspect the hydroxymethyl bridgehead substitution to interfere with the reaction. The other, more probable theory, is an electronic effect imparted on the substrate caused by the halide to prevent C-O bond insertion of the Rh(I) species, inhibiting the process.

Scheme 1-50 Proposed rationale for failure of the ring-opening onto oxabicycles containing vicinal halogens



The precedent for the halide effect illustrated in Scheme 1-20 upon reaction of unsymmetrical oxabicycle **1.076** containing a chloro and a methoxy group, forming a single regioisomer. This product resulted from C-O bond insertion adjacent to the methoxy group. This result suggests an electronic bias for regioselective ring-opening. It is known[61] that oxabicycles containing halides on the 3,4 positions of the aromatic ring undergo ring-opening reactions, likely because they have influence on the C-O insertion given their distance (Scheme 1-51). Given the novelty of the halide substitution pattern, an investigation was warranted to isolate the reasoning for this.

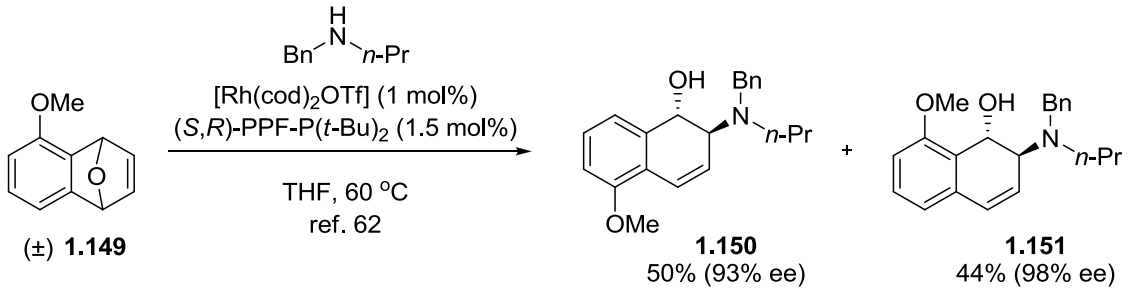
Scheme 1-51 Known oxabicyclic ring-opening conditions for halogen substitution



[61] Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444; Lautens, M.; Fagnou, K. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5455.

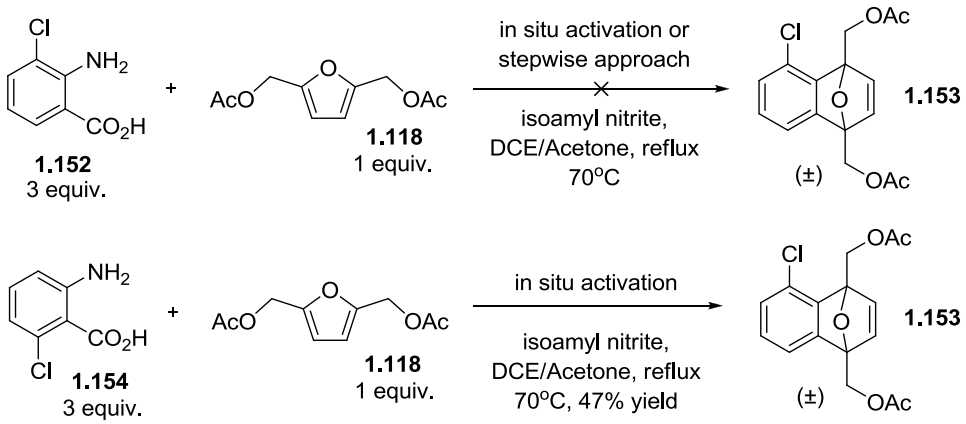
With the help of Patrick Franke, the idea achieving a regiodivergent resolution of unsymmetrical oxabicycle **1.149** was probed (Scheme 1-52).[62] The use of a monohalogenated oxabicycle analogously may enable ring-opening, but would suffer from a 50% yield maximum as only one desirable isomer would be made.

Scheme 1-52 Regiodivergent resolution of unsymmetrical **1.149** using various aliphatic amines



Monochloro oxabicycle **1.153** was prepared through an aryne DA of mono-chloro anthranilic acid. The reaction did not proceed using **1.152**, by either by the *in situ* activation or the stepwise process as the diazonium salt was not formed. Structural isomer **1.154** on the other hand generated **1.153** in 47% yield (Scheme 1-53).

Scheme 1-53 Franke's synthesis of mono-chloro substituted oxabicycles



The ring-opening conditions were then explored (Table 1-2). Once again, the substrate proved unreactive. Additional ring-opening studies on dichlorosubstituted oxabicycle **1.148** were

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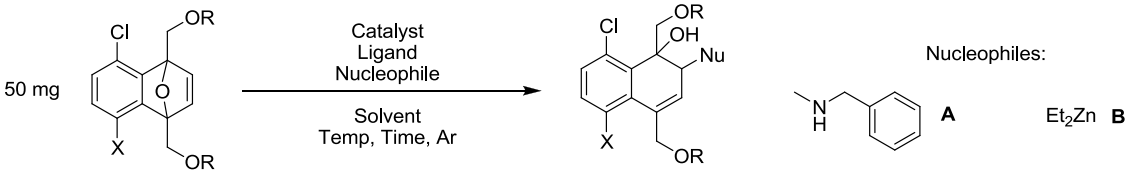
[62] Webster, R.; Boyer, A.; Fleming, M.J.; Lautens, M. *Org. Lett.* **2010**, *12*, 5418.

attempted but with no success. Reactions with diethyl zinc as a nucleophile did not render the starting material in any way. This was surprising as decomposition was expected given the reactivity alkyl zinc reagents. The high cost of the mono-chloro anthranilic acid precursor discouraged further exploration of this route. It may prove fruitful to try the ARO using an amine nucleophile on **1.153** to verify that these do not open as only the intramolecular epoxidation conditions were tried.

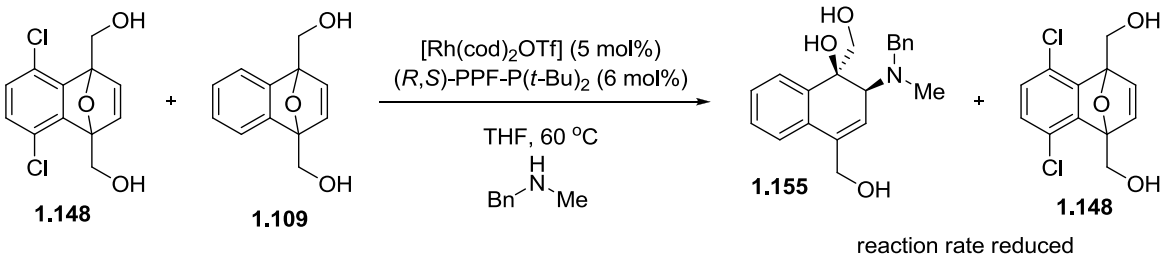
Table 1-2 Franke's screen of ring-opening conditions



Entry	X	R	Catalyst (mol %)	Ligand (mol %)	Nucleophile (equiv.)	Comments	T	Time	Result
1	Cl	OAc	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**none**	epoxide, THF	80 °C	1 h	NR
2	Cl	OAc	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**none**	epoxide, THF	80 °C	16 h	NR
3	Cl	OAc	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**none**	stoichiometric, THF	25 °C	16 h	NR
4	Cl	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**none**	stiochiometric, THF	25 °C	16 h	NR
5	H	OAc	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**none**	epoxide, THF	80 °C	1 h	NR
6	H	OAc	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**none**	epoxide, THF	80 °C	16h	NR
7	H	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**none**	epoxide, THF	80 °C	1 h	NR
8	H	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**none**	epoxide, THF	80 °C	16 h	NR
9	Cl	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	stoichiometric, THF	80 °C	16 h	NR
10	Cl	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	DMF	80 °C	1 h	NR
11	Cl	OH	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**A** (1.1)	DMF	80 °C	16 h	NR
12	Cl	OH	$Pd(dppf)Cl_2$ (5)	none	**B** (1.1)	DCM	25 °C	16 h	NR
13	Cl	OH	$Pd(dppf)Cl_2$ (5)	none	**B** (1.1)	DCM	60 °C	16 h	NR

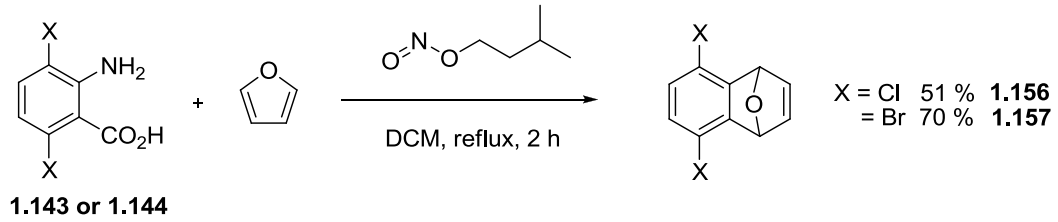
A stoichiometric reaction of **1.148** was attempted but failed (Table 1-2). A competition study of **1.148** with the parent oxabicycle **1.109** was conducted to evaluate if the **1.148** inhibited the ring-opening of **1.109** (Scheme 1-54). While **1.109** reacted, it did not react as quickly as in the absence of **1.148**.

Scheme 1-54 Competition study of the oxabicyclic ring-opening reaction



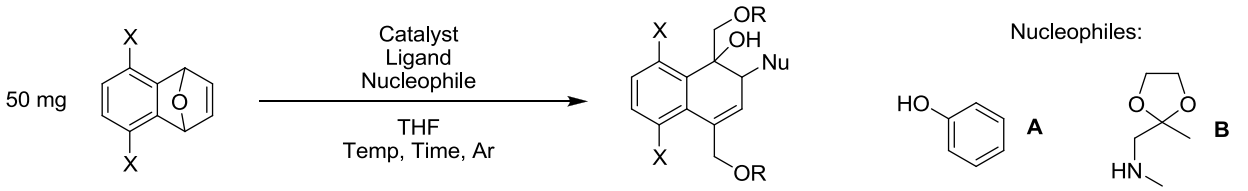
1.148 was simplified by removing the bridgehead substitution to isolate the reasoning for the lack of reactivity. Dichloro- and dibromo-oxabicycles **1.156** and **1.157** were prepared by an aryne DA cycloaddition using distilled furan (Scheme 1-55). The susbtrates were subjected to previous ring-opening conditions using phenolic nucleophiles[63] (Table 1-3). The failure to react implied that the electronic influence of the halide substituents on those aromatic positions hinders the Rh(I) from inserting into the oxabicyclic bridgehead C-O bond. To confirm that the bridgehead had no negative effect on the ring-opening, a control reaction using $Rh(cod)_2OTf$ / Josiphos catalyst system onto **1.156** tested for this, which was unreactive (Table 1-3, entry 5).

Scheme 1-55 Synthesis of halogenated oxabicycles lacking a hydroxymethyl bridgehead



[63] Lautens, M.; Fagnou, K.; Yang, D.Q. *J. Am. Chem. Soc.* **2003**, *125*, 14884.

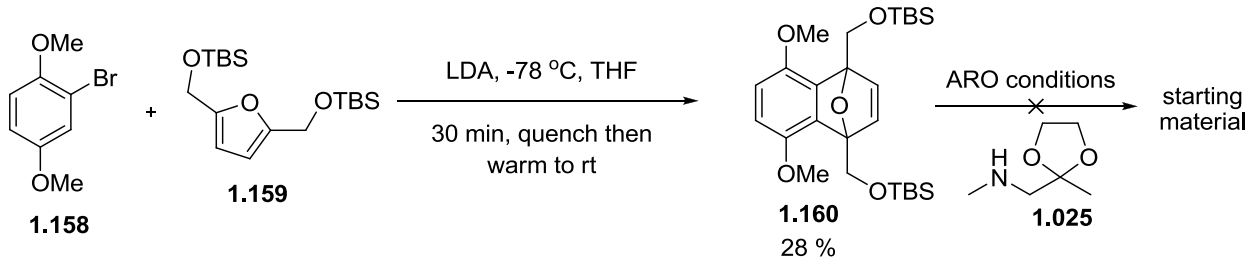
Table 1-3 Ring-opening screen of halogenated oxabicycles lacking bridgehead substituents



Entry	X	Catalyst (mol %)	Ligand (mol %)	Nucleophile (equiv.)	Comments	T	Time	Result
1	Cl	$[Rh(cod)Cl]_2$ (2.5)	dppf (5)	**A** (4)	none	80 °C	4 h	NR
2	Br	$[Rh(cod)Cl]_2$ (2.5)	dppf (5)	**A** (4)	none	80 °C	4 h	NR
3	Cl	$[Rh(cod)Cl]_2$ (2.5)	dppf (5)	**A** (4)	using substrate **1.148**	80 °C	4 h	NR
4	OMe	$[Rh(cod)Cl]_2$ (2.5)	dppf (5)	**A** (4)	control	80 °C	4 h	52%
5	Cl	$Rh(cod)_2OTf$ (5)	(*R*,*S*) JosiPhos (6)	**B** (1.1)	none	60 °C	8 h	NR

Given these findings, it was decided that the halogenated oxabicycles were not suitable for ARO. To address the electronic effect issue, it was necessary to substitute the halogens for an electron donating substituent to probe if this transformation can be done. Bismethoxy oxabicycle **1.160** was prepared by an aryne DA of furan **1.159** with benzyne precursor **1.158**, formed through deprotonation with LDA and subsequent elimination of the bromide. Oxabicycle **1.160** was isolated in poor yields after multiple attempts[64] (Scheme 1-56).

Scheme 1-56 Preparation of dimethoxy substituted oxabicycles and initial ring-opening

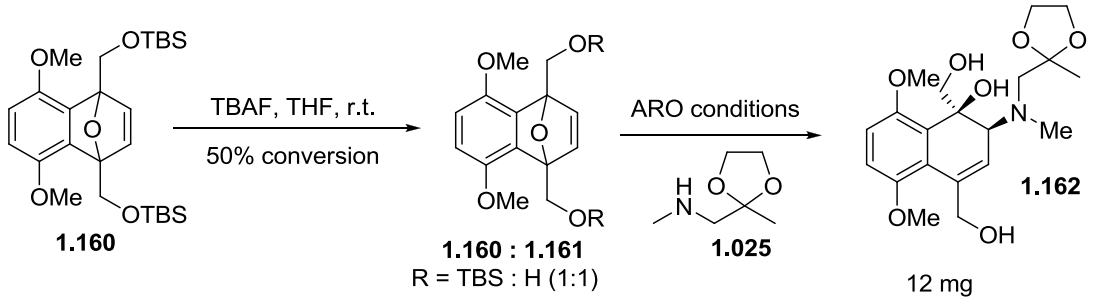


Functionalized oxabicycle **1.160** failed to undergo ring-opening using amine nucleophile **1.025**. Suspecting the protection hindered the reaction, the recovered starting material was

[64] Repeated attempts gave average yields of 7 – 15% at -78 °C and lower yields at 0 °C. Best yield was obtained with commercial LDA at 28%.

subjected to desilation conditions to furnish crude oxabicycle **1.161** (Scheme 1-57). In an attempt to prevent loss of the product, the crude was subjected to the ring-opening conditions given the small amount of isolated material (~50 mg, 1:1 ratio of **1.160**:**1.161)**. The ARO of **1.161** did furnish ring opened product **1.162**, and 12 mg was obtained by column chromatography. The product was confirmed by ^{1}H, ^{13}C NMR, IR, and HRMS. The yield for this reaction is estimated at 50% based on the amount of starting material in the crude mixture.

Scheme 1-57 Successful ring-opening **1.161** using an aliphatic amine



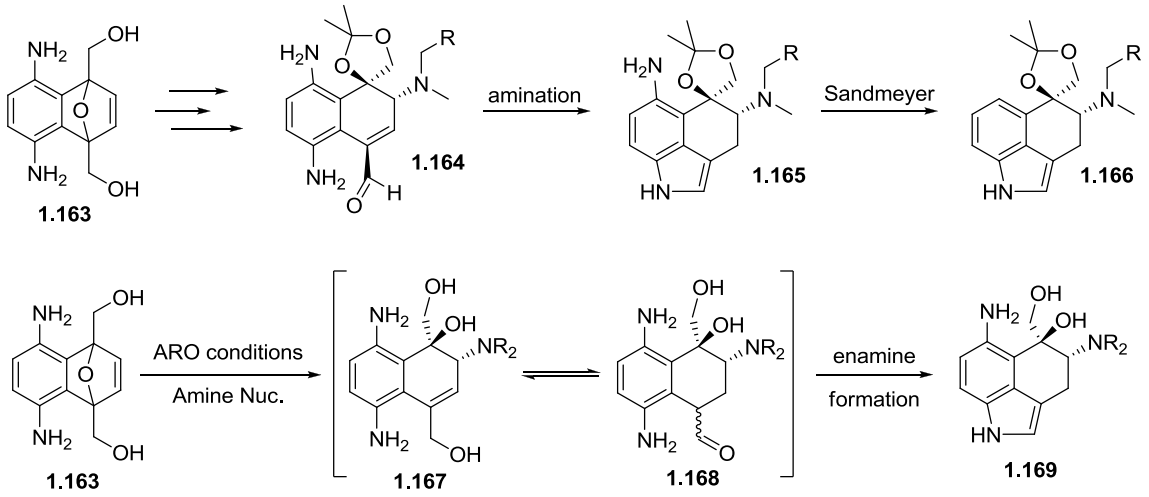
This finding confirms that the substitution pattern of the aromatic positions adjacent to the oxabicyclic alkene influences the capacity of the Rh-catalyzed ARO to operate based on electronics. Having halide substituents rendered the substrate too inert, whereas electron-donating substituents promoted the reaction. To this effect, it was necessary to devise a new strategy by modifying the oxabicyclic precursor to bear electron-donating groups in a way to allow for ring-opening, while at the same time be capable of functionalization by a pendant amine.

1.3.3 Towards the Synthesis of Oxabicyclic Precursors containing Electron-Donating Groups

Two new routes were proposed for the construction of the **ABC** fused tricyclic core of **1.015**. The first uses a disubstituted amine already in place on oxabicycle **1.163**, to form the indole by an amine condensation of a pendant aldehyde **1.164**. (Scheme 1-58). The precedent for

similar cyclizations have been demonstrated previously.[65] This process may operate in tandem given rhodium's ability to oxidize the allylic alcohol **1.167** to aldehyde **1.168** under prolonged lactonization conditions. The proximal amine would be a likely candidate for the ring closure, precluding lactonization. Once **1.165** or **1.169** is constructed, the free amine can be oxidized and cleaved under protic Sandmeyer conditions. Since there are no examples of benzofused-oxabicycles containing aromatic amines, this is likely the biggest challenge faced when pursuing this route.

Scheme 1-58 Proposed synthetic route of **ABC** fused ring-system using bis-amine oxabicycles

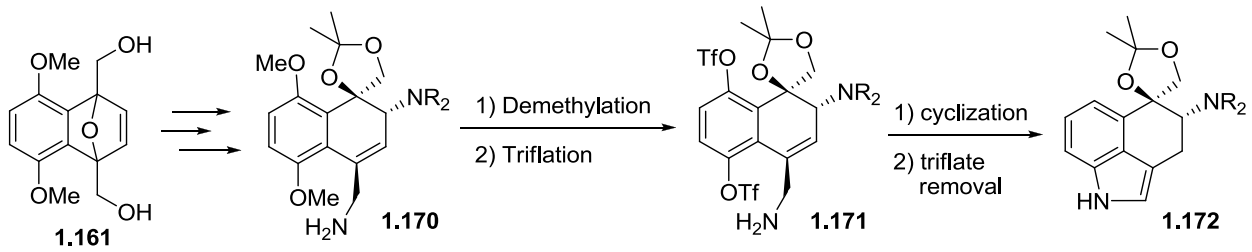


The second route utilizes the already established reactivity of oxabicycle **1.161** (Scheme 1-59). This sequence is unattractive given the low yielding aryne DA reaction to prepare **1.161**. Nonetheless, this intermediate is known to operate in ARO and it would be a suitable candidate for the synthesis if the yield can be better optimized. **1.161** could be modified using either ARO or lactonization, followed by reduction to yield intermediate **1.170**. After acetonization of the diol, displacement of the pendant alcohol to an amine, demethylation of the OMe group, and subsequent triflation, intermediate **1.171** would be suited for cross-coupling of the amine to the

[65] Xu, F.; Simmons, B.; Reamer, R.A.; Corley, E.; Murry, J.; Tschaen, D. *J. Org. Chem.* **2008**, *73*, 312; Ikawa, T.; Fujita, Y.; Mizusaki, T.; Betsuin, S.; Takamatsu, H.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Org. Biomol. Chem.* **2012**, *10*, 293.

sp^2-triflate using standard Pd(II) conditions.[66] Once the indole is constructed, the triflate can be reductively cleaved.[67] Although this synthetic route is within reach, the indole formation would require many more steps overall than the scheme proposed earlier.

Scheme 1-59 Proposed route using dimethoxy oxabicycles to form **ABC** fused ring-system



Efforts to probe the former strategy would be worthwhile if successful, and was pursued first. Initial studies probed the possibility of obtaining **1.163** directly by aminating dichloro oxabicycle **1.148**, but were unsuccessful (Table 1-4). Various literature reports[68] showed precedent for the amination of aryl halides of similar nature, but this was not applicable to **1.148**. Time did not permit a full investigative study and more work with the dibromo oxabicycles should be done as they are more apt to amination conditions.

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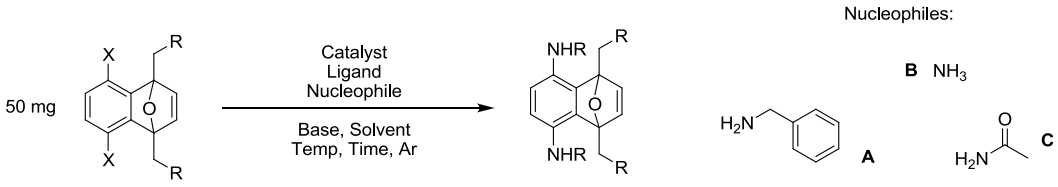
[66] Louie, J.; Driver, M.; Hamann, B.; Hartwig, J. *J. Org. Chem.***1997**, *62*, 1268; Wolfe, J.; Buchwald, S. *J. Org. Chem.* **1996**, *61*, 1133.

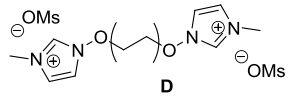
[67] Martínez, A.G.; Alvarez, R.M.; Aguirre, J.A.; Subramanian, L.R. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1595.

[68] (a) Panteleev, J.; Zhang, L.; Lautens, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 9089. (b) See ref. 63. (c) Lundgren, R.J.; Peters, B.D.; Alsabeh, P.G.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4071. (d) Xu, H-J.; Liang, Y-F.; Cai, Z-Y.; Qi, H-X.; Yang, C-Y.; Feng, Y-S. *J. Org. Chem.* **2011**, *76*, 2296. (e) Hu, Y-L.; Wang, P-C.; Chen, T.; Lu, M. *J. Chin. Chem. Soc.* **2010**, *57*, 604.

Table 1-4 Screen of conditions to aminate dihalogenated oxabicycles



Entry	X	R	Catalyst (mol %)	Ligand (mol %)	Nucleophile (equiv.)	Base (equiv.)	Comments	T	Time	Result
1	Cl	OAc	$Pd(OAc)_2$ (5)	X-Phos (10)	**A** (2.5)	Cs_2CO_3 (1.4)	Tol / ref. 68a	100 °C	16 h	NR[a]
2	Cl	OAc	$Pd(OAc)_2$ (5)	X-Phos (10)	**A** (2.5)	Cs_2CO_3 (1.4)	Tol / ref. 68a	130 °C	16 h	NR[a]
3	Cl	OH	$Pd(OAc)_2$ (5)	X-Phos (10)	**A** (2.5)	Cs_2CO_3 (1.4)	Tol / ref. 68a	100 °C	16 h	NR
4	Cl	OTBS	$Pd(OAc)_2$ (5)	X-Phos (10)	**A** (2.5)	Cs_2CO_3 (1.4)	Dioxane / ref. 68a	100 °C	16 h	NR
5	Cl	OTBS	$Pd(OAc)_2$ (5)	X-Phos (10)	**A** (2.5)	Cs_2CO_3 (1.4)	Dioxane / ref. 68a	130 °C	16 h	NR
6	Cl	OAc	$Pd_2(dba)_3$ (5)	BINAP (6)	**A** (2.5)	Cs_2CO_3 (1.4)	Tol / ref. 68b	130 °C	16 h	NR[a]
7	Cl	OTBS	$Pd_2(dba)_3$ (5)	BINAP (6)	**A** (2.5)	Cs_2CO_3 (1.4)	Tol / ref. 68b	130 °C	16 h	NR
8	Br	OAc	[Pd(cinnamyl)Cl]$_2$ (5)	Mor-DalPhos (10)	**B** (4)	NaO^{t}Bu (2)	NH_3 in MeOH Dioxanes / ref. 68c	80 °C	16 h	NR[a]
9	Cl	OAc	CuI (20)	none	**C** (2.5)	K_2CO_3 (2)	DMF	130 °C	16 h	NR[a]
10	Br	OAc	CuI (10)	none	**B** (10)	NH_4OH (10)	(n-Bu)$_4$NOH (2 eq) ref. 68d	130 °C	16 h	decomp.
11	Cl	OAc	$CuSO_4$ H_2O (50)	none	**B** (2.5)	NH_4OH (2.2)	MeCy / ref. 68e additive **D**	60 °C	16 h	NR[a]



D
PEG_{1000}-DIL

a – deprotection of OAc was observed

Attention was turned to the preparation of diamino benzyne precursors, or their related nitro compounds. Various precursors to generate arynes have been pursued towards the preparation of **1.163**. For the interested reader, a review[69] of aryne use in natural product synthesis is referenced.

We attempted to prepare singly substituted amine **1.175** to probe the likelihood that a diamine aryne precursor is suitable (Scheme 1-60). The proposed route required ortho TMS/OTf nitrobenzene **1.174**, which is either reduced to the amine prior to or after an aryne DA is performed. **1.174** would be made by **1.173** in a 3-step *o*-bromination, triflation, and TMS exchange sequence.

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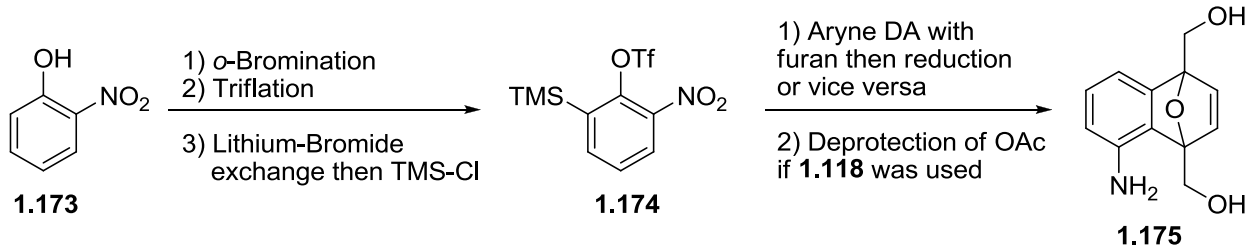
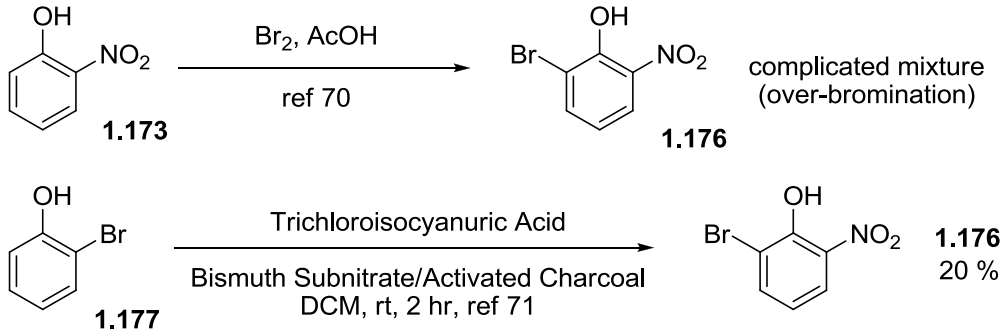
[69] Tadross, P.M.; Stoltz, B.M. *Chem. Rev.* **2012**, *112*, 3550.

Scheme 1-60 Proposed route to form aniline oxabicycle **1.175** using TMS/OTf precursor



Methods to prepare intermediate **1.176** from **1.173** by bromination,[70] or nitration[71] resulted in low yield (Scheme 1-61). Using commercial **1.176** instead, TMS exchange of the bromide to form **1.178** was difficult (Scheme 1-62). Literature conditions[72] for the TMS protection of 2-bromophenol failed on **1.176**. Another attempt to modify **1.176** by lithium-bromide exchange followed by quenching with TMS-Cl was unsuccessful; however, the lithiated species did react to install an *n*-Bu substitutent **1.179,** likely because the alkyl bromide formed *in situ* was more electrophilic than the TMS-Cl. This synthetic route was abandoned to try others.

Scheme 1-61 Studies towards the preparation of **1.174**

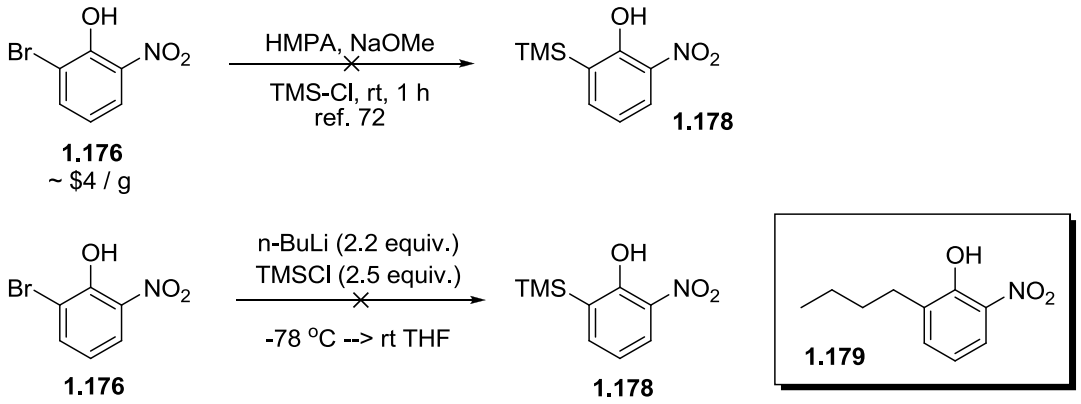


[70] Zhao, S-H, Berger, J. et al. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3504.

[71] Pourali, A.R.; Fatemi, F. Chin. Chem. Lett. **2010**, 1283.

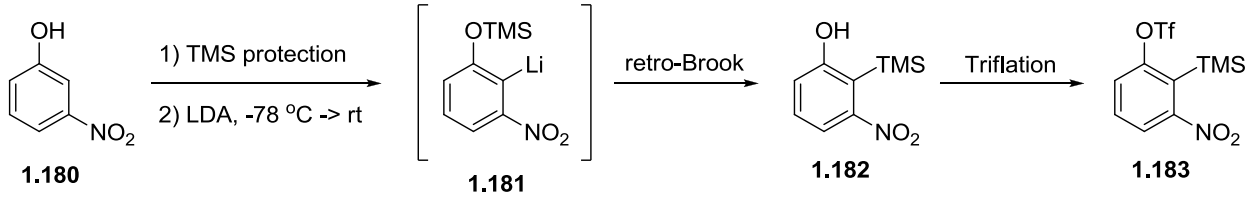
[72] Nishide, K.; Ohsugi, S-I.; Miyamoto, T.; Kumar, K.; Node, M. *Monatschefte für Chemie* **2004**, *135*, 189.

Scheme 1-62 Studies towards TMS protection of **1.174**



The second approach was to prepare structural isomer **1.183** without the necessity to functionalize the bromide (Scheme 1-63). By protecting **1.180** with TMS, a retro-Brook rearrangement[73] could occur upon treatment with LDA to furnish **1.182**. The regioselectivity of the lithiation would not be guaranteed as there is no precedent for substrates bearing a nitro group.

Scheme 1-63 Proposed route to TMS/OTf precursor containing one nitro group



Subjecting **1.180** to standard silation conditions was unsuccessful (Scheme 1-64). A second attempt by deprotonation followed by trapping with TMSCl did not work, but the *n*-Bu group was incorporated. A procedure[74] to silate **1.180** was later realized, but time did not permit another attempt. It may be worthwhile to revisit this route as lithiation was demonstrated to be selective between the nitro and hydroxyl groups and the possibility for a retro-Brook to occur when using LDA as base still exists.

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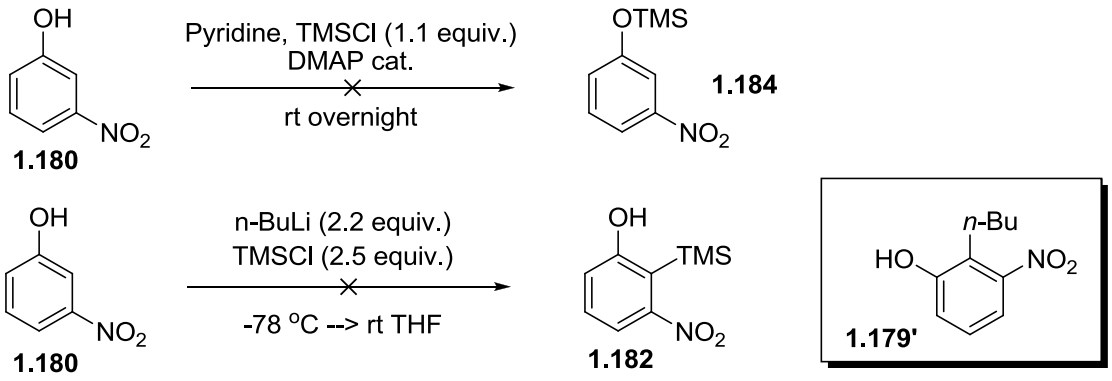
[73] Shankaran, K.; Snieckus, V. *Tetrahedron Lett.* **1984**, *25*, 2827.

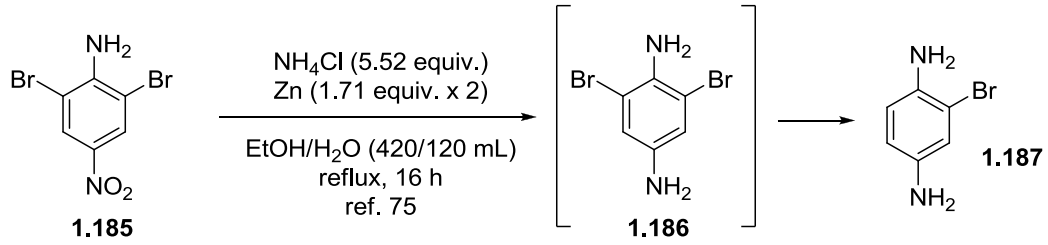
[74] Candito, D., *Ph.D. Thesis*, University of Toronto, **2012**. Using HMPA, LDA, THF – reflux, overnight.

Scheme 1-64 Attempt to TMS protect directly and effect a silyl transfer through a retro-Brook



Attention was turned to the preparation of diamine substrates. As the preparation of tetrasubsituted aromatic compounds tended to be difficult, it would challenging to prepare an ortho TMS/OTf benzyne precursor containing two aromatic amines. A literature procedure to prepare **1.187** using a one-pot reduction has been reported,[75] which was encouraging as the starting material is commercially available (Scheme 1-65).

Scheme 1-65 Preparation of diamino aryne precursor



Initial attempts to reproduce these results, yielded dibrominated intermediate **1.186** in 30% yield as opposed to 82%. By resubjecting **1.186** to the same conditions, desired product **1.187** was accessed, albeit in lower overall yield than the reported 67%. Both amines must be protected to carry out the aryne DA; otherwise, a large excess of LDA is required, and the substrate may not be stable upon multiple deprotonations. Protection with Boc or Cbz did not give adequate conversion and another group was tried.

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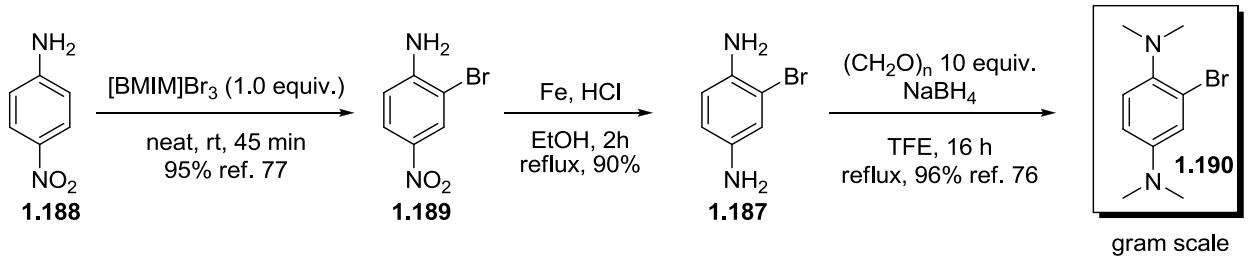
[75] Schwarzenbacher, G.; Evers, B.; Schneider, I.; de Raadt, A.; Besenhard, J.; Saf, R. *J. Mater. Chem.* **2002**, *12*, 534.

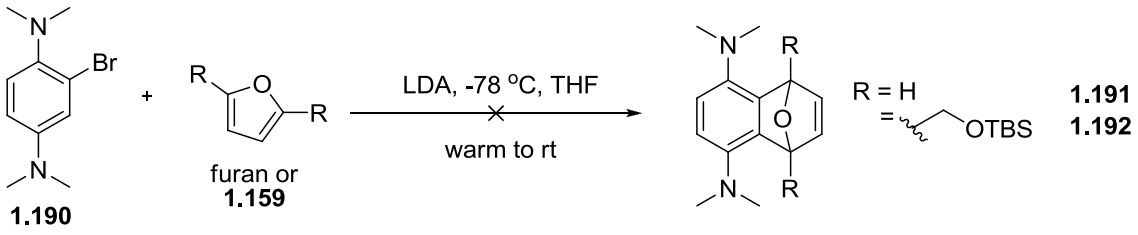
A literature procedure[76] to bis-N-methylate **1.187** in a one-pot reductive amination using paraformaldehyde gave **1.190** quantitatively (Scheme 1-66). Although the diamino precursor **1.187** was made in low yield, a better synthetic route was realized by bromination of **1.188** using an ionic liquid,[77] which furnished **1.189** in 95% yield. Reduction of **1.189** provided **1.187** in greater overall yield.

Scheme 1-66 Improved route to forming protected diamino aryne precursors



Attempted cycloadditions using **1.190** were unreactive (Scheme 1-67). Furthermore, it is also uncertain how reliably the methyl groups can be deprotected. Precedent for the demethylation of N,N-dialkyl aryl amines has been demonstrated.[78] For this reason the route was abandoned.

Scheme 1-67 Aryne DA attempt using protected diamino bromobenzene



Given the difficult nature of preparing benzofused oxabicycles containing aromatic amines, this strategy was viewed to be difficult. Attention was turned to the use of anisole fused oxabicycles.

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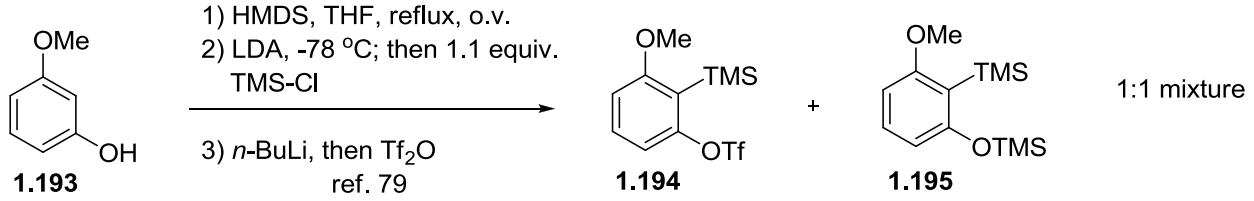
[76] Tajbakhsh, M.; Hosseinzadeh, R.; Alinezhad, H.; Ghahari, S.; Heydari, A.; Khaskar, S. *Synthesis* **2011**, *3*, 490.

[77] Le, Z-G.; Chen, Z-C.; Hu, Y.; Zheng, Q-G. *Synthesis* **2004**, *17*, 2809.

[78] Murahashi, S-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.***1983**, *105*, 5002.

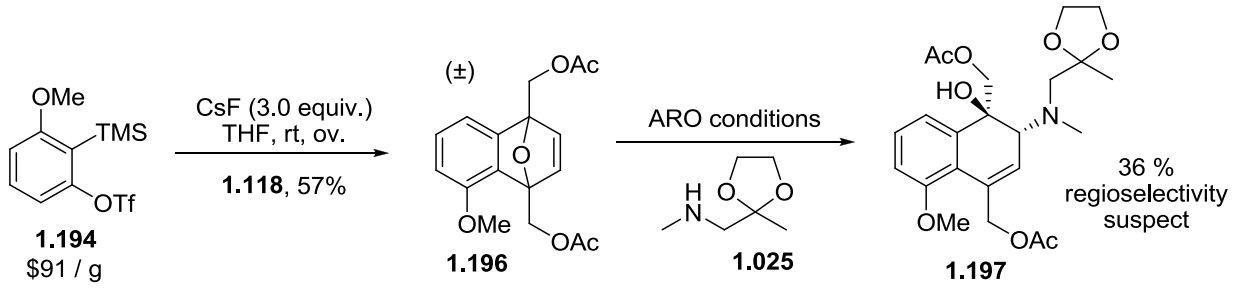
As **1.158** was difficult in aryne DA cycloaddition, unsymmetrical **1.194** was sought after instead to probe if the yield can be imrpoved. A literature route to prepare **1.194** exists;[79] however, a complex mixture of intermediate **1.195** and **1.194** resulted as **1.195** did not proceed to completion (Scheme 1-68). **1.194** was difficult to isolate because of separation issues.

Scheme 1-68 Attempt to prepare anisole based TMS/OTf aryne precursor



1.194 was obtained commercially instead, and testing this with **1.118**, furnished cycloaddition product **1.196** in 57 % yield. When **1.196** was subjected to ARO, **1.197** was isolated in 36% yield, confirming that these substrates are amenable to ring-opening[80] (Scheme 1-69). The regioselectivity depicted in **1.197** is not entirely confirmed as 2-D NMR suggests the formation of the other regioisomer. More studies to elucidate the structure are needed. Although the yield for the cycloaddition improved, this route was too costly. Unless a viable method to prepare *meso*-dimethoxy oxabicycle is developed, this route would be too unattractive given the maximal yield of 50% resulting from a regiodivergent resolution.

Scheme 1-69 Tsoung's successful cyclization and ARO of **1.196**



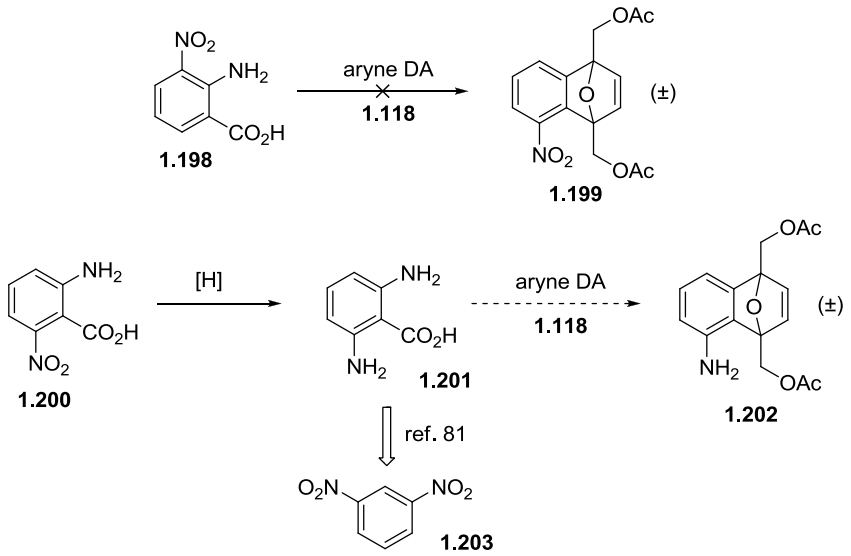
[79] Pena, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem. Int. Ed.* **1998**, *37*, 2659.

[80] The preparation of **1.196** along with the ring-opening condition was conducted by Jennifer Tsoung, Ph.D. student.

The preparation of either methoxy or amine substituted oxabicycle has been a very arduous pursuit. The potential to use an an anthranilic acid was pursued with the hope that it furnish *meso*-oxabicycles.

Commercial anthranilic acid **1.198** was subjected to aryne DA conditions, **1.198** was unreactive, likely for the same reason that the mono-chloro oxabicycle **1.152** was unsuccessful (Scheme 1-70). As the structural isomer **1.200** was not available, a alternate method to pursue this aryne precursor may be worthwhile. Another strategy to form **1.202** directly would be to use reduced **1.201**, and generate benzyne regardless where it is formed given its symmetry. A patented procedure exists for the preparation of **1.201** from **1.203**.[81]

Scheme 1-70 Attempt to prepare aniline fused oxabicycle along with a proposed novel route



The limitation of the anthranilic strategy is that only one amine can be substituted. If pursuing a bis-amine symmetrical aryne precursor, both amines would require a protection strategy to avoid formation of the undesired benzyne isomers. One potential way to circumvent this is to prepare **1.205** using a literature procedure to nitrate[82] **1.204** towards the preparation of anthranilic acid **1.207**, and employ and aryne DA is possible (Scheme 1-71). This route was not successful likely because the aromatic ring was too electron deficient to carry out the Friedel-

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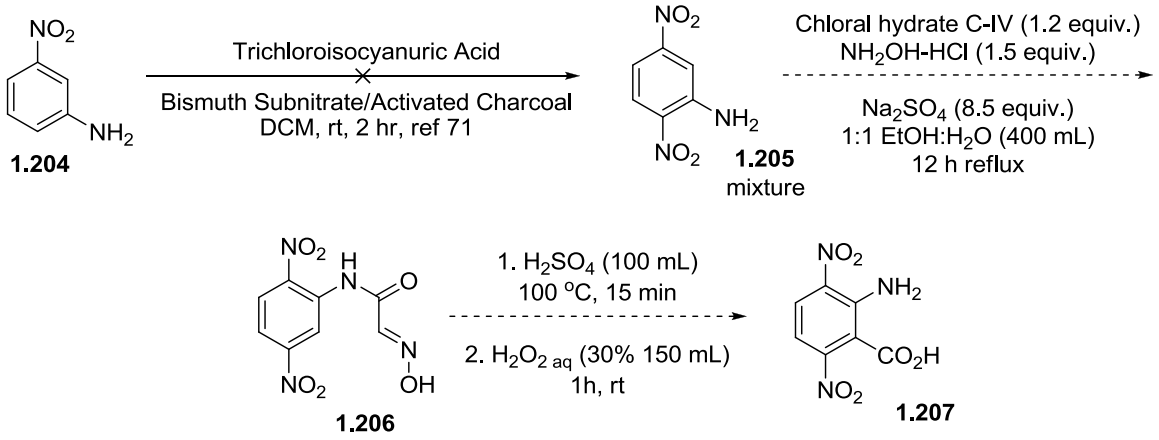
[81] Krantz, A.; Robin, S.; Tim, T. US4657893 A1, **1987**.

[82] See ref. 68.

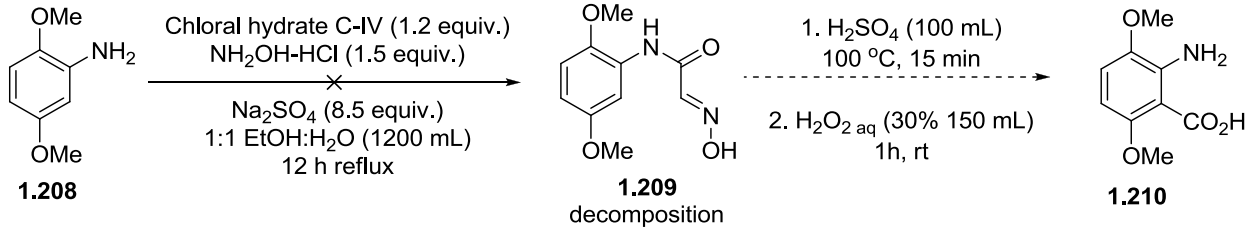
Crafts cyclization. Further, the likelihood of generating benzyne at a later stage would be suspect because of its electronic character.

Scheme 1-71 Attempt to prepare dinitro anthranilic acid



Since preparation of the diamino anthranilic acid was unsuccessful, dimethoxy anthranilic acid **1.210** was pursued from **1.208** (Scheme 1-72). Despite multiple efforts, including a second similar procedure,[83] **1.209** could not be isolated and the product decomposed under the conditions, making this route not viable.

Scheme 1-72 Attempt to prepare dimethoxy substituted anthranilic acid



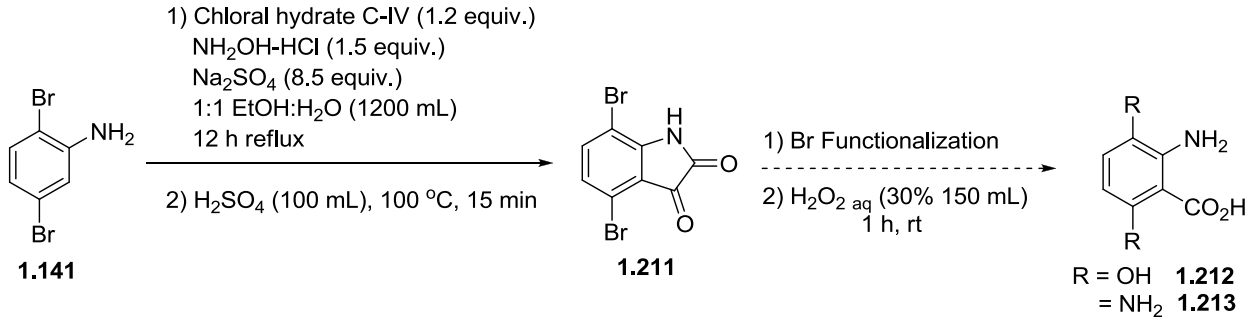
[83] Wilcox Jr., C.F.; Farley, E.N. *J. Am. Chem. Soc.***1984**, *106*, 7195.

1.4 Future Directions

Ultimately, among the many iterative attempts to prepare various oxabicycles bearing EDG, the nominally yielding aryne DA reaction of **1.158** with furan **1.159** to form dimethoxy oxabicycle **1.161** remains to be the best and only successful candidate for this synthesis (Scheme 1-59). However, the need for improved yields warrants a thorough investigation, as the present yield is not acceptable at this early stage. Unless the present reaction is optimized, an entirely new synthetic scheme may have to be devised.

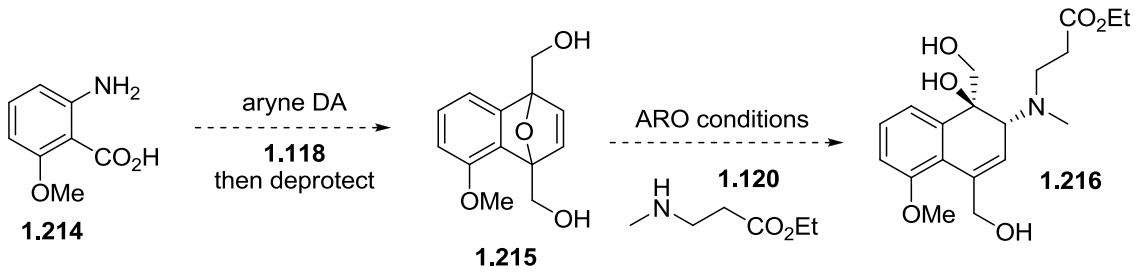
One idea that may be successful, is to intercept dihalo isatin intermediate **1.211** and functionalize the halides with an amine or an alcohol, following oxidative base hydrolysis to furnish anthranilic acid **1.212** or **1.213** (Scheme 1-73). Any necessary modification, such as a protection, can be done before liberating the anthranilic acid.

Scheme 1-73 Proposed functionalization of dibromo isatin towards novel anthranilic acids



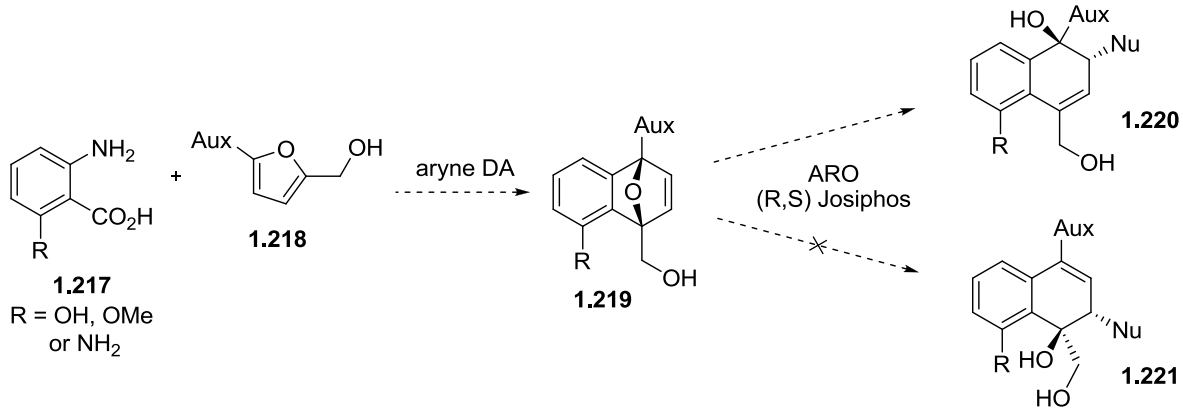
Additionally, commercial anthranilic acid **1.214** should be tested as a precursor to mono-methoxy oxabicycle **1.215** (Scheme 1-74). This intermediate would quickly assess the viability of **1.214** as a substrate, and if successful, can be used on scale as the substrate is relatively inexpensive. Although a regiodivergent resolution would limit the yield, improved preparation of the oxabicycle would be sufficient reason to avoid the desymmetrization approach in exchange for higher throughput.

Scheme 1-74 Suggested synthetic route using anisole based anthranilic acid



The formation of diastereomerically pure oxabicycle **1.219** using tethered furan **1.218**, analogously to the preparation of diastereoselective azabicycles using a camphorsultam tether,[84] has potential to bias one regioisomer upon ARO by catalyst control (Scheme 1-75). The nucleophilic attack on **1.219** would be indirectly based on the chirality of the catalyst system, provided a high degree of diastereoselectively during the C-O insertion of the bridgehead. Thus, based on the configuration of the starting material, enantiomerically pure **1.015** could be accessed without suffering from a maximal yield of 50% during ARO because of a regiodivergent resolution.

Scheme 1-75 Proposed synthesis of diastereoselective oxabicycles using a chiral tether

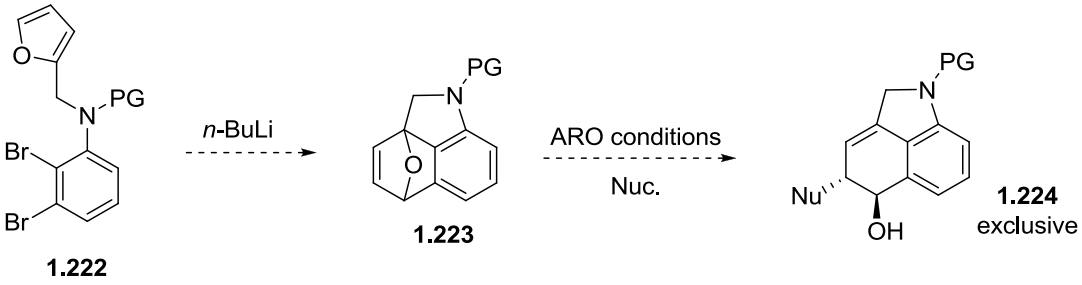


It may be possible to carry out an intramolecular aryne DA to form fused **ABC** oxabicyclic intermediate **1.223** with the indoline already fused (Scheme 1-76). Treatment of **1.223** to ring-opening would be regioselective as Rh would insert into the tertiary bridgehead

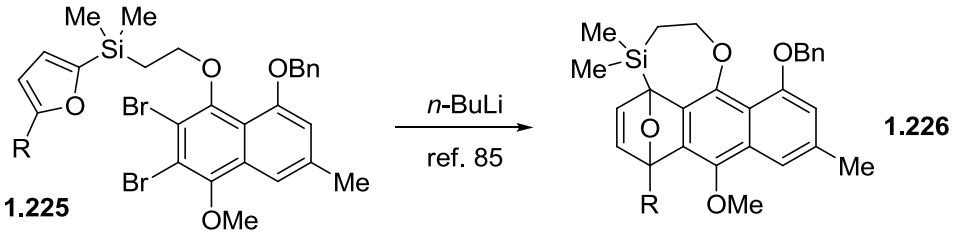
[84] Webster, R.; Lautens, M. *J. Org. Chem.* **2009**, *11*, 4688.

substituted carbon preferentially. This is a potentially elegant strategy towards the direct formation of fused **1.224**. Precedent for this cyclization with a larger ring system exists in the literature[85] (Scheme 1-77), in which tricyclic fused oxabicycle **1.226** was prepared. An attempt using this strategy was unsuccessful likely because the 2-furyl position of **1.228** was prone to lithiation under benzyne DA condition (Scheme 1-78). This idea should be revisited to explore the potential of this route.

Scheme 1-76 Proposed intramoecular annulation of a tricyclic fused oxabicycle using a furyl tether

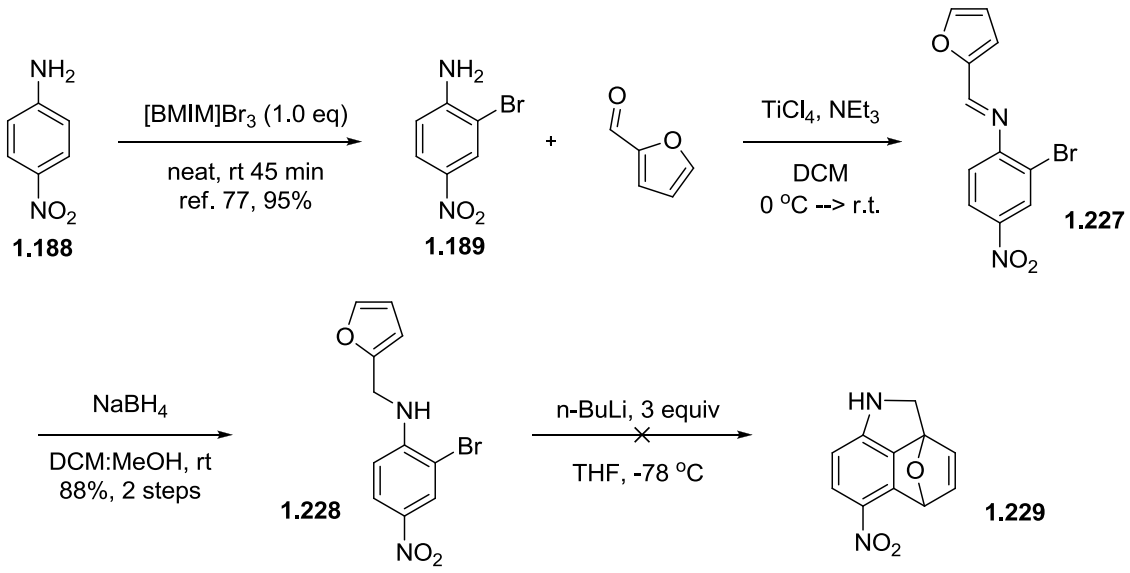


Scheme 1-77 Martin's precedent for the formation 6,6,7-fused tricyclic oxabicycles



[85] O'Keefe, B.M.; Mans, D.M.; Kaelin, D.E.; Martin, S.F. *Tetrahedron* **2011**, *67*, 6524.

Scheme 1-78 Attempted intramolecular cyclization using a furyl tether



To sum, a total synthesis using an ARO remains an attractive strategy as the key ARO step is an already established method. ARO was reliable in unsubstituted oxabicycles, and oxabicycles bearing electron-donating groups. Many lessons were learned about the lack of reactivity of halogenated substrates, which added more insight to the previous observation[86] on the electronic influence of the substrate on the ability of Rh to insert into the bridgehead C-O bond. This electronic effect warrants further mechanistic investigation on the reasoning by using computational studies to map the electron density at the bridgehead carbons. Preparation of aryne precursors was met with a lot of difficulty given their novelty. With more investigation to this end, the preparation of a viable aryne precursor reliably may be realized very soon, to which the synthesis should be carried out smoothly. A number of recommendations has been highlighted throughout this discussion, and it may also be worthwhile to revisit the parent oxabicycle, as the potential to successfully C-H aminate would provide the most efficient route possible. In all, this expedition has been a very insightful one and there is high hope that the ARO strategy can very well provide **1.015** in a stereoselectively elegant fashion in the near future.

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[86] Lautens, M.; Fagnou, K. *Proc. Nat. Acad. Sci.* **2004**, *101*, 5455.

Experimental Information

General Considerations

General Experimental Procedures: Unless otherwise stated, reactions were carried out under argon atmosphere in sealed oven-dried glassware with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel canula. Organic solutions were concentrated by rotary evaporation at 23–40 °C under 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was carried out on pre-coated SIL G/UV254 (0.2 mm) plates from EM Separations. Visualization was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, anisaldehyde or in potassium permanganate ($KMnO_4$), followed by heating using a heat gun. Purification of reaction products were generally done by flash chromatography with Silicycle™ Ultra-Pure 230–400 mesh silica gel.

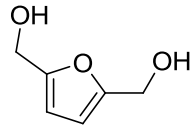
Materials: Tetrahydrofuran (THF) was distilled under nitrogen from Na/benzophenone; triethylamine was distilled from KOH; dichloromethane was passed through a column of activated alumina under nitrogen. $Rh(cod)_2OTf$ was used as received from Strem Chemicals; Josiphos ligands were provided by Solvias AG: (*R*)-1-[(*S*P)-2-(diphenylphosphino)ferrocenyl]ethyldi-tert-butylphosphine is referred to as (*R*,*S*p)-Josiphos; (*S*)-1-[(*R*P)-2-(diphenylphosphino)ferrocenyl]ethyldi-tert-butylphosphine is referred to as (*S*,*R*p)-Josiphos. The amines *N*-methyl-1-(2-methyl-1,3-dioxolan-2-yl)-methanamine and ethyl 3-(methylamino)propanoate were prepared according to literature procedures. All other amines were purified by distillation before use or purchased from the Sigma-Aldrich Chemical Company and used immediately. Furfuryl alcohol and furfural was purified by distillation before use.

Instrumentation: Melting points were recorded using a Fisher–Johns melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at room temperature using a Varian Gemini-300, Unity-400 or Mercury 400 spectrometer. ^1H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and ^{13}C spectra were referenced to solvent (77.23 ppm for $CDCl_3$). No special notation is used for equivalent carbons. IR spectra were obtained using a

Shimadzu FTIR-8400S spectrometer in $CHCl_3$ as thin films on NaCl plates. High resolution mass spectra were obtained using an ABI/Sciex Qstar mass spectrometer (ESI).

Oxabicyclic Alkene Synthesis

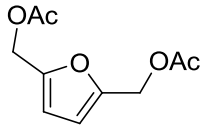
Furan Precursors:



1.117

n-BuLi (2.5 M in hexanes, 204 cm^3, 510 mmol, 2.5 equiv.) was added slowly to a stirred solution of furfuryl alcohol (20 g, 204 mmol, 1.0 equiv.) in THF (250 cm^3) at −78 °C. The reaction mixture was stirred at −78 °C for 30 minutes then at rt for 30 minutes before being re-cooled to −78 °C. A slurry of paraformaldehyde (30.6 g, 1.02 mol, 5.0 equiv.) in THF (250 cm^3), previously dried over 4 Å molecular sieves and degassed for 1 hr, was added by addition funnel slowly and the reaction mixture was stirred at −78 °C, then allowed to reach ambient temperature overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl (200 cm^3) and the reaction mixture was extracted with EtOAc (6 × 200 cm^3). The combined organic layers were dried (magnesium sulfate) and concentrated *in vacuo* to give the title compound (12.5 g, 97.9 mmol, 48%) as a pale yellow solid. The crude product was used without further purification. Range of reproduced yields (50 – 60%)

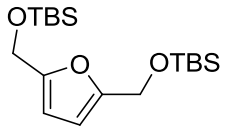
m.p. 69–71 °C (lit. 74–75); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.14 (s, 2H), 4.45 (s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.9, 108.4, 56.6; **IR ν_{max}** 3349, 2927, 2869, 1697, 1560, 1412, 1412, 1243, 1195, 1010 cm^{-1}; The recorded data were in accord with those reported in S. Goswami, S. Dey, S. Jana, *Tetrahedron* **2008**, *64*, 6358.



1.118

Acetyl chloride (15.3 cm3, 215 mmol, 2.2 equiv.) was added slowly to a stirred solution of crude **1.117** (12.5 g, 98 mmol, 1 equiv.) and NEt_3 (29.9 cm^3, 215 mmol, 2.2 equiv.) in DCM (500 cm^3) at 0 °C using a 2L round bottom flask. The reaction mixture was stirred at ambient temperature for 3 h then the reaction was quenched by the addition of saturated aqueous NH_4Cl (300 cm3). The aqueous layer was extracted with EtOAc (2 × 300 cm3) and the combined organic layers were dried (magnesium sulfate) and concentrated *in vacuo*, and purified with silica gel (10:90 EtOAc:Hexanes, isocratic) to give the title compound (20 g, 98 mmol, 97%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (s, 2H), 5.01 (s, 4H), 2.06 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.5, 150.1, 111.5, 58.0, 20.8; **IR ν_{max}** 3114, 1728, 1437, 1376, 1355, 1235, 1020 cm^{-1}; The recorded data were in accord with those reported in Fotso, S.; Maskey, R. P.; Schroeder, D.; Ferrer, A. S.; Laatsch, H.; Gruen-Wollny, I. *J. Nat. Prod.* **2008**, *71*, 1630.



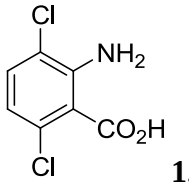
1.159

To a solution of **1.117** (1.5 g, 11.7 mmol, 1.0 equiv.) in THF (10 mL) were added imidazole (1.36 g, 19.9 mmol, 1.7 equiv.) and TBDMSCl (3.88 g, 25.8 mmol, 2.2 equiv.) at 0 ^oC. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc and washed with water and brine. The organic layers were combined, dried over MgSO4, filtered, and concentrated in vacuo. The crude yellow oil was purified over silica (0 – 10% EtOAc in Hexanes) to afforded the desired product as a clear oil (3.76 g, 10.5 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (s, 1H), 4.61 (s, 2H), 0.90 (s, 9H), 0.08 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 153.9, 107.8, 58.2, 25.9, 18.4, -5.2; The recorded data were in accord with those reported in Rubin, Y.; Chuang, S-C. et al. *J. Org. Chem.* **2007**, *72*, 2716.

General Method for Anthranilic Acid:

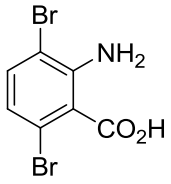
Chloral hydrate (120-190 mmol, 1.2 equiv.), 2,5-dihaloaniline (100 – 160 mmol, 1.0 equiv.), hydroxylamine hydrochloride (149 - 235 mmol, 1.5 equiv.), and Na_2SO_4 (0.8 - 1.3 mol, 8.5 equiv.) were suspended in a mixture of H_2O (600 cm^3) and EtOH (600 cm^3). The mixture was stirred and kept at reflux for 12 h. The solution was then concentrated by evaporation of the ethanol and the flask immersed in an ice bath for 1h, which caused precipitation of a brown to grey solid. The suspension was filtered, and the crystals were air dried to provide crude 2,5-dihaloisonitrosoacetanilide. This crude was then directly cyclized by heating at 100 ^oC in 86% H_2SO_4 for 15 min. The resulting dark red suspension was poured onto crushed ice to yield 3,6-dihaloisatine as a bright orange powder. To a stirred suspension of the crude isatin in 5 % NaOH (150 cm^3) is added 30 % H_2O_2 (150 cm^3) dropwise. The reaction mixture was stirred at 50 ^oC for 1 hr and then allowed to reach room temperature. The filtered solution was acidified to pH 4 with 1 M HCl, and the solid product collected by filtration without further purification.



1.144

The title compound product was obtained as an orange solid (19 g, 92 mmol, 59%).

m.p. 148 – 150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.5 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.4, 146.5, 133.7, 132.7, 119.2, 118.9, 112.5; **IR ν_{max}** 3472, 2533, 1663, 1453, 1254, 634; **HRMS** (ESI) Calculated [M] $C_7H_5Cl_2NO_2$: 205.9776, Found: 205.9776.



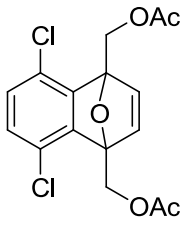
1.143

The title compound product was obtained as a grey solid (12.9 g, 44 mmol, 44%).

m.p. 120 – 121 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 4.77 (s, 1H), 3.94 (br s, 2 H) **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.7, 146.6, 135.9, 133.6, 123.3, 122.2, 122.0**; IR ν_{max}** 3377, 3073, 2359, 1699, 1609, 1447, 1250, 793; **HRMS** (ESI) Calculated [M] $C_7H_5Br_2NO_2$: 293.8765, Found: 293.8773.

General Method for Oxabicycle Formation:

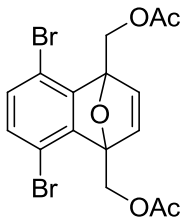
A solution of 3,5-dihaloanthranilic acid (2 equiv.) in acetone (15 cm^3) was added drop-wise over 1 hour to a stirred solution of furan **1.118** or distilled furan (1 equiv.), and iso-pentyl nitrite (2 equiv.) in dichloromethane (20 cm^3) while refluxing. The reaction mixture was stirred under reflux for 4 hours then concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (0 to 20% EtOAc in Hexanes) to furnish the dihalooxabicycle.



1.146

The title compound was isolated as a pale yellow solid (5.0 g, 14.1 mmol, 60%).

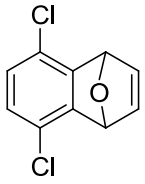
m.p. 92–95 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.95 (s, 2H), 6.91 (s, 2H), 5.07 (d, J = 12.9 Hz, 2H), 5.03 (d, J = 12.9 Hz, 2H), 2.12 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.8, 148.3, 144.0, 129.1, 125.2, 92.1, 61.3, 20.8; **IR ν_{max}** 1739, 1436, 1367, 1230, 1052, 899, 736; **HRMS** (ESI) Calculated [$M+Na^+$] $C_{16}H_{14}Cl_2NaO_5$: 379.0092, Found 379.0116.



1.145

The title compound was obtained as a tan solid (2.2 g, 4.9 mmol, 83%).

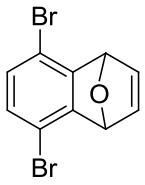
m.p. 109–110 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.99 (s, 2H), 6.94 (s, 2H), 5.10 (d, J = 12.9 Hz, 2H), 5.02 (d, J = 12.9 Hz, 2H), 2.13 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.9, 150.8, 144.0, 132.2, 113.5, 92.4, 61.2, 20.9; **IR ν_{max}** 1744, 1441, 1367, 1227, 1051, 897, 756; **HRMS** (ESI) Calculated $[M+Na^+]$ $C_{16}H_{14}Br_2NaO_5$: 466.9080, Found 466.9106.



1.156

The title compound was obtained as a tan oil (800 mg, 3.75 mmol, 51%).

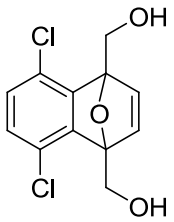
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (s, 2H), 6.87 (s, 2H), 5.90 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.3, 142.8, 127.5, 124.8, 82.0; The recorded data were in accord with those reported in Shahlai, K.; Hart, H. *J. Org. Chem.* **1981**, *54*, 2615.



1.157

The title compound was isolated as a brown oil (1.56 g, 5.2 mmol, 70 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 2H), 6.84 (s, 2H), 5.76 (s, 2H); The recorded data were in accord with those reported in Stringer, M.B.; Wege, D. *Tetrahedron Lett.* **1980**, *21*, 3831.

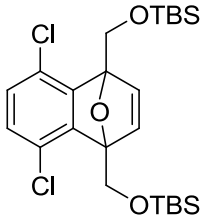


1.148

Sodium methoxide (227 mg, 4.2 mmol, 1 equiv.) was added to a solution of OAc protected oxabicycle (1.5 g, 4.2 mmol, 1.0 equiv.) in methanol (10 cm^3). The reaction mixture was stirred at ambient temperature for 30 min then quenched by the addition of saturated aqueous NH_4Cl (10 cm^3). The mixture was extracted with EtOAc (3 × 10 cm3) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude was recrystallized in 9:1 EtOH:H_2O and filtered to isolate the title compound was as a white solid (1.11 g, 4.1 mmol, 97%).

m.p. 106–108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.96 (s, 2H), 6.88 (s, 2H), 4.59 (s, 4H), 2.36 (br s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 148.9, 144.3, 128.9, 124.9, 94.8, 60.4; **IR ν_{max}** 3397, 1444, 1105, 1057, 991, 859, 736; **HRMS** (ESI) Calculated [M+Na^+] $C_{12}H_{10}Cl_2NaO_3$: 294.9892, Found 294.9905.

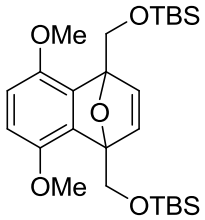
Formation of TBS protected Oxabicycles:



(From Table 1-4)

To a solution of **1.148** (200 mg, 0.73 mmol, 1.0 equiv.) in THF (10 mL) were added imidazole (85 mg, 1.24 mmol, 1.7 equiv.) and TBDMSCl (243 mg, 1.61 mmol, 2.2 equiv.) at 0 ^oC. The reaction mixture was stirred at room temperature for 2 h. It was then diluted with EtOAc and washed with water and brine. The organic layers were combined, dried over MgSO4, filtered, and concentrated in vacuo then purified on a silica column (0 – 10 % EtOAc in Hexanes) to furnish the title product as a white solid (300 mg, 0.60 mmol, 82%).

m.p. 65 – 66 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.82 (s, 1H), 4.70 (d, J = 12.1 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 0.91 (s, 9H), 0.11 (d, J = 7.7 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.1, 144.1, 128.4, 124.8, 94.8, 61.0, 25.9, 18.4, -5.1, -5.3**; IR ν_{max}** 2930, 2857, 1472, 1256, 1111, 1005, 835; **HRMS** (ESI) Calculated [M+ NH_4^+] $C_{24}H_{42}Cl_2NO_3Si_2$: 518.2080, Found 518.2071.

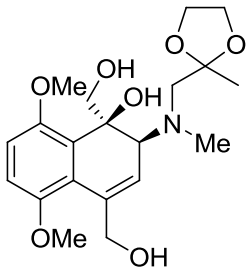


1.160

Commercial LDA (3.85 cm^3, 2 M, 5.5 equiv.) was slowly added to a clear solution of furan **1.159** (500 mg, 1.40 mmol, 1 equiv.) and benzyne precursor **1.158** (1.05 cm^3, 7.01 mmol, 5 equiv.) in anhydrous THF (15 cm^3) at -78°C. The solution turned dark brown in colour and was left to warm to room temperature overnight. The resulting light brown solution was then quenched with saturated NH_4Cl, extracted with EtOAc (3 x 10 cm^3), washed with brine, dried with $MgSO_4$, filtered, and the combined organics concentrated in vacuo. The crude was purified by flash chromatography (20% EtOAc in Hexanes, isocratic) to give the title compound as a white solid (200 mg, 0.41 mmol, 29%).

m.p. 60 – 61 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.52 (s, 1H), 4.82 (d, J = 12.3 Hz, 1H), 4.36 (d, J = 12.3 Hz, 1H), 3.73 (s, 3H), 0.93 (s, 9H), 0.12 (d, J = 2.5 Hz, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.9, 144.0, 139.2, 111.6, 94.4, 61.7, 56.2, 26.0, 18.5, -5.0, -5.3; **IR ν_{max}** 2930, 2857, 1495, 1254, 1059, 999, 835, 777; **HRMS** (ESI) Calculated [M+H^+] $C_{26}H_{45}O_5Si_2$: 493.2806, Found 493.2792.

Asymmetric Ring-Opening Conditions:

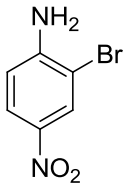


1.162

THF (1.2 cm^3) was added to a mixture of $Rh(cod)_2OTf$ (2.2 mg, 5 mol%), (*R*,*S*)-Josiphos (3.1 mg, 6 mol%) in a Teflon-lined screw-top vial. The vial was flushed with Ar, sealed and stirred at ambient temperature for 10–20 mins. The catalyst solution was transferred to a solution of crude oxabicyclic diol **1.161** (est. 25 mg, 0.1 mmol, 1 equiv.) and amine **1.025** (13.6 mg, 1.1 equiv.) in THF (1.2 cm^3) in a Teflon-lined screw-top vial. The vial was sealed and the contents heated to 60 °C for 16 h. The reaction was allowed to reach ambient temperature and transferred to a round-bottomed flask with EtOAc. The crude solution was concentrated to dryness, re-dissolved in the minimum volume of EtOAc and directly purifying by column chromatography (20:77:3 EtOAc:Hexanes:MeOH, isocratic) furnished the title compound as a white solid (19 mg, 0.05 mmol, 50%).

m.p. 155 – 156 ^oC; $\mathbf{[\alpha]_D^{28}}$ -0.71^o (c = 0.3, $CHCl_3$) ; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.86 (d, J = 3.8 Hz, 1H), 6.23 (d, J = 3.8 Hz, 1H), 4.43 (d, J = 8.4 Hz, 1H), 4.01 (s, 2H), 3.95 (s, 2H), 3.84 (s, 6H), 2.94 (d, J = 14.2 Hz, 1H), 2.80 (d, J = 14.1 Hz, 1H), 2.45 (s, 3H), 1.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.3, 150.2, 137.0, 128.3, 125.7, 123.6, 113.1, 113.0, 110.2, 104.8, 77.6, 68.8, 66.2, 65.6, 64.7, 64.6, 64.0, 56.7, 56.5, 40.7, 22.8; **IR ν_{max}** 3374, 2938, 2884, 1480, 1260, 1045, 733; **HRMS** (ESI) Calculated $[M+H^+]$ $C_{20}H_{30}NO_7$: 396.2022, Found 396.2011.

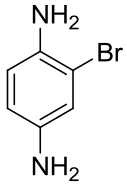
Towards Oxabicycles bearing EDGs:



1.189

Br_2 (0.37 cm^3, 7.2 mmol, 1.0 equiv.) was added neat [bmim]Br (1.59 g, 7.24 mmol, 1 equiv.) in a 100 mL round bottom flask and left to stir under reduced pressure via aspirator for 2 h until the solution turned a deep red colour ([bmim]Br_3). To this liquid was added arylamine **1.188** (1 g, 7.24 mmol, 1 equiv.) and continuously stirred for 1 h at room temperature. The reaction mixture was directly purified by recrystallization with EtOH (95%) to give the title compound as a yellow solid (1.5 g, 6.88 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 2.5 Hz, 1H), 8.01 (dd, J = 2.5, 8.9 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 4.10 (br s, 2H); The recorded data were in accord with those reported in Le, Z-G.; Chen, Z-C.; Zheng, Q-G. *Synthesis.* **2004**, *17*, 2809.

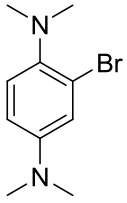


1.187

1.189 (4.5 g, 20.7 mmol, 1 equiv.), iron powder (5.3 g, 95 mmol, 4.6 equiv.), concentrated HCl (15.9 cm^3 37%), and ethanol (70 cm^3) were combined together and heated to reflux for 1 h with stirring. Once cooled, the solution was poured into a separatory funnel containing ether (150 cm^3) and 2 N NaOH (75 cm^3). The organic layer was collected, washed with water (2 x 50 cm^3) and brine (50 cm^3), dried over $MgSO_4$, and filtered. The solvent was removed to leave a brown oil, which was not further purified (3.5 g, 18.7 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (d, J = 2.5 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.51 (dd, J = 2.5, 8.4 Hz, 1H), 3.53 (br s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.2, 136.3, 119.3, 117.0,

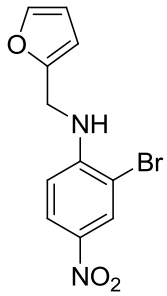
116.2, 110.3; The recorded data were in accord with those reported in Schwarzenbacher, G.; Evers, B.; Schneider, I.; de Raadt, A.; Besenhard, J.; Saf, R. *J. Mater. Chem.* **2002**, *12*, 534.



1.190

In a round-bottomed flask (100 mL) equipped with magnetic stirrer and a condenser, a mixture of **1.187** (1.6 g, 8.55 mmol, 1.0 equiv.) and paraformaldehyde (1.8 g, 60 mmol, 7 equiv.) in TFE (15 mL) was prepared. Then, $NaBH_4$ (1.3 g, 34 mmol, 4 equiv.) was added and the mixture was stirred under reflux conditions overnight. The mixture was filtered through celite and the filtrate concentrated. The crude was purified by column chromatography over silica gel (20% EtOAc in Hexanes) to furnish the product as a tan solid (2.0 g, 8.23 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, J = 8.8 Hz, 1H), 6.96 (d, J = 2.9 Hz, 1H), 6.66 (dd, J = 2.9, 8.8 Hz, 1H), 2.89 (s, 6H), 2.72 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.9, 141.8, 121.1, 121.0, 117.7, 112.5, 45.0, 40.9; The recorded data were in accord with those reported in Schwarzenbacher, G.; Evers, B.; Schneider, I.; de Raadt, A.; Besenhard, J.; Saf, R. *J. Mater. Chem.* **2002**, *12*, 534.



1.228

To a solution of furfural aldehyde (0.49 g, 5.07 mmol, 1.1 equiv), **1.189** (1 g, 4.61 mmol, 1.0 equiv) and NEt_3 (1.93 cm^3, 13.8 mmol, 3.0 equiv) in DCM (15 cm^3, 0.3 M) was added $TiCl_4$ in DCM (4.6 cm^3, 4.61 mmol, 1.0 equiv) slowly at 0 ^oC. After stirring at 0 ^oC for 30 min, the

solution was left to stir overnight and gradually warm to room temperature. This followed by removal of TiO_2 by celite filtration and the filtrate was concentrated. The residue was redissolved in toluene and NEt_3HCl was removed by filtration through celite. The organic was removed in vacuo and imine **1.227** was used without further purification. **1.227** was redissolved in a 1:1 solution of DCM:MeOH (10 cm^3). To it was added $NaBH_4$ (192 mg, 1.1 equiv.) and the reaction was left to stir at room temperature overnight. The solution was quenched with sat. NH_4Cl and then extracted with DCM (3 x 15 mL). The organic was collected, dried using $MgSO_4$, filtered and removed in vacuo. The crude was subjected to column chromatography (10% EtOAc in Hexanes, isocratic) to afford the title compound as a yellow solid (1.2 g, 4.07 mmol, 88%).

m.p. 84 – 85 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.6 Hz, 1H), 8.07 (ddd, J = 0.5, 2.6, 9.1 Hz, 1H), 7.39 (dd, J = 0.8, 1.8 Hz, 1H), 6.70 (d, J = 9.1 Hz, 1H), 6.35 (dd, J = 1.9, 3.2 Hz, 1H), 6.30 (dd, J = 0.8, 3.2 Hz, 1H), 5.48 (br s, 1H), 4.48 (d, J = 5.7 Hz, 2H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.0, 149.2, 142.6, 128.7, 127.4, 125.1, 110.5, 109.2, 108.0, 107.9, 40.8**; IR** $\mathbf{v_{max}}$ 3401, 1589, 1504, 1323, 1119, 744; **HRMS** (ESI) Calculated $[M+H^+]$ $C_{11}H_{10}Br_1N_2O_3$: 296.9875, Found 296.9872.

Chapter 2: Expeditious Synthesis of Molecular Motors and Switches

2.1 Introduction

2.1.1 Preface

All of the work presented in this chapter has been published.[87] This was done in collaboration with Hongqiang (Patrick) Liu, a former postdoc. All of my contributions will be specifically highlighted throughout, and the characterization information for my compounds is provided. Information in this chapter is reprinted, and adapted, with permission from the American Chemical Society (© 2012 – ref 87a), and John Wiley & Sons, Inc. (© 2012 – ref 87b).

2.1.2 Background on Tetrasubstituted Helical Alkenes

Definition of Molecular Motors and Switches

- Molecular Motors

A molecular motor is a class of molecules typically found in nature which consumes energy and converts it into usable motion or mechanical work. This is characterized by rotary motion about an axis of rotation, finding its application biochemically in protein-based motors responsible for propelling *E. coli*, among many other biophysical examples.[88] These motors tend to be more energy efficient than life-sized motors as they operate in a thermal bath, where the fluctuations due to thermal noise are significant enough to have these motors turn. They may also require the energy of a high-energy bond, like the phosphate bonds of ATP, to function. Given these mechanical operations occur in nanometer environments, this process loses less energy in the form of heat than their macro counterparts because the amount of work that they do is so

---

[87] (a) Liu, H.; El-Salfiti, M.; Lautens, M. *Org. Lett.* **2012**, *14*, 3648. (b) Liu, H.; El-Salfiti, M.; Lautens, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 9846.

[88] (a) Bustamante C.; Chemla, Y.R.; Forde, N.R.; Izhaky, D. *Annu. Rev. Biochem.* **2004**, *73*, 705. (b) Nelson, P.; Radosavljevic, M.; Bromberg, S. "*Biological physics"* Freeman: **2004**.

small, in the order of piconewtons.[89] Thus, collectively, their combined power as molecular machines is of interest given the potential to revolutionize technology as newer materials will allow the development of smaller electronic devices along with directed drug delivery.[90] The prospect of synthetic molecular motors was first raised by nanotechnology pioneer Richard Feynman in 1959 in his talk, "There's Plenty of Room at the Bottom".[91]

The requirement for a synthetic molecular motor is that it is to undergo unidirectional rotation about a 360^{o} axis of rotation up on the consumption of energy. The first two examples have been established by T.R. Kelly and coworkers, using a chemically driven motor, and by B.L Feringa and coworkers, using a light-driven molecular motor. Both published[92] in 1999 in the same issue of Nature. Kelly and coworkers used a three-bladed triptycene rotor **2.001**, the mobile fragment, and a helicene stator (Scheme 2-1). The system was demonstrated to rotate 120^{o} over 5 steps. Upon conversion of the amine to an isocyanate by condensation with phosgene, **2.002** is formed which then spontenously rotates about the axis to bring the isocyanate group in close proximity to the hydroxyl tether on the helicence, reacting to form the cyclic carbamate **2.003**. This intermediate irreversibly traps the intermediate in this conformational state, which is higher in energy and close to its rotational barrier. Supplementing a small amount of energy, **2.004** then overcomes the helical strain barrier to furnish **2.005**. Cleavage of the carbamate liberates the free amine and alcohol **2.006**. This elegant example highlights how chemical energy can be utilized to control unidirectional motion. However, the group has not been able to extend the system so that this transformation is repeatable.[93]

---

[89] Bamrungsap, S.; Phillips, J.A.; Xiong, X.; Kim, Y.; Wang, H.; Liu, H.; Hebard, A.; Tan, W. *Small* **2011**, *7*, 601.

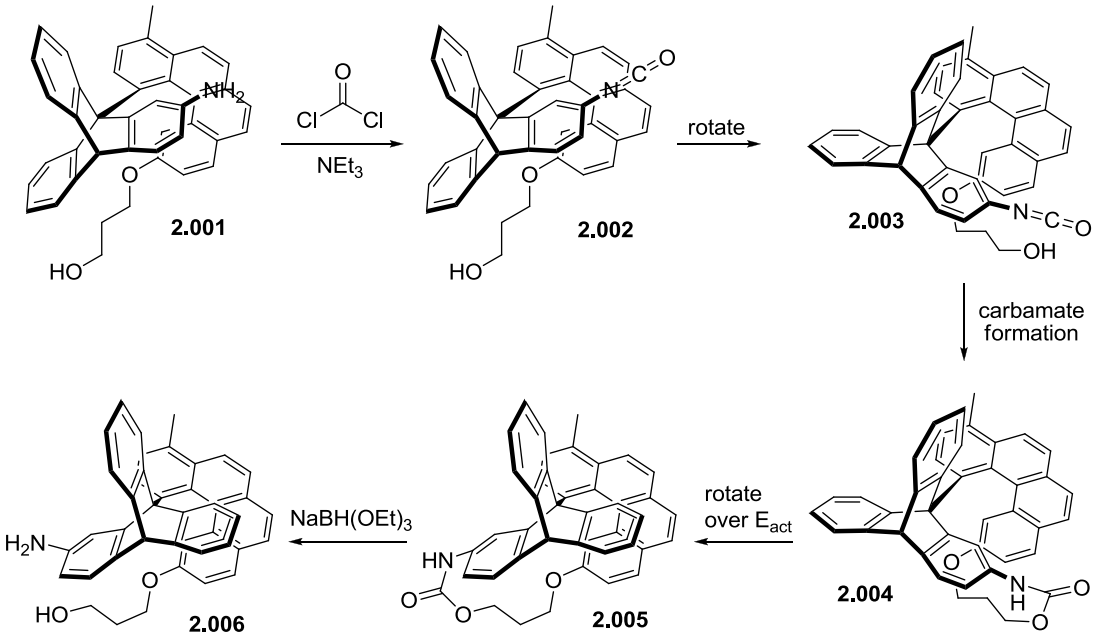
[90] Cohen-Karni, T.; Langer, R.; Kohane, S. *ACS Nano* **2012**, *6*, 6541.

[91] "Nanovision: Engineering the Future" Milburn, C. Duke University Press: **2008**.

[92] (a) Kelly, T.R.; De Silva, H.; Silva, R.A. *Nature*, **1999**, 150. (b) Koumura, N.; Zijlstra, R.W.J.; van Delden, R.A.; Harada, N.; Feringa, B.L. *Nature*, **1999**, 152.

[93] Kelly, T.R.; Cai, X. et al. *J. Am. Chem. Soc.* **2007**, *129*, 376.

Scheme 2-1 Chemically driven rotation of a molecular motor by Kelly's group



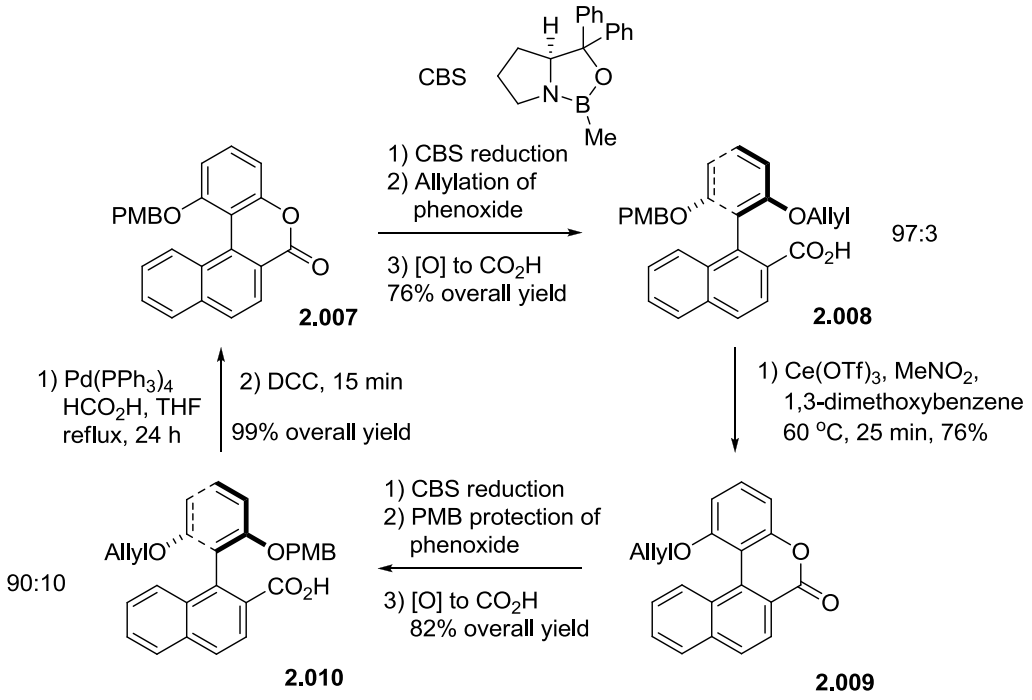
Since then two additional examples of chemically driven rotary motors have been described. They employ a stereoselective ring opening of a racemic biaryl lactone by the use of chiral reagents, which results in a directed 90^{o} turn with each operation. Branchaut and coworkers reported[94] this approach to accomplish a 180^{o} rotation, albeit non-repeatable. Feringa and coworkers followed suit[95] by demonstrating 360^{o} motion repeatedly using this concept onto their biaryl lactone system **2.007** (Scheme 2-2). Steps 1 and 3 are asymmetric ring opening reactions to control the direction of the aryl rotor and steps 2 and 4 consist of chemoselective deprotections followed by regioselective lactonization. This is the only reported example of a chemically driven artificial molecular motor capable of 360^{o} motion.

---

[94] Lin, Y.; Dahl, B.J.; Branchaud, B.P. *Tetrahedron Lett.* **2005**, *46*, 8359.

[95] Fletcher, S.P.; Dumur, F.; Pollard, M.M.; Feringa, B.L. *Science*, **2005**, *310*, 80.

Scheme 2-2 Feringa's improved chemically driven 360° rotation of biaryl compounds



The second class of synthetic molecular motors established is that of Feringa's light driven tetrasubstituted helical alkenes. This is discussed in Section 1.2.2. Since then another class of molecular motors emerged, the single-molecule electric motor measuring at 1nm,[96] which was developed by a team of researchers, headed by E.C.H. Sykes, at the Tufts University School of Arts and Sciences. A single butyl methyl sulphide molecule is adsorbed onto a Copper (1,1,1) single crystal and measured using a scanning electron microscope asymmetrically, which was found to rotate in one direction upon monitoring the position of butyl tail over time. The rotation rate was controlled by actuating electron flux or by temperature. The asymmetrical surface of the crystal plane is believed to impart the barrier of rotation upon the S-Cu bond, whereby the sulphur can bind using one of two of its lone pairs.[97] Such remarkable developments in the nanosciences are promising as applications of these systems may be put to practice in the near future.

---

[96] Sykes, E.C.H.; Tierney, H.L. et al. *Nature Nanotech.* **2011**, *6*, 625.

[97] Baber, A.E.; Tierney, H.L.; Sykes, E.C.H. *ACS Nano* **2008**, *2*, 2385.

- Molecular Switches

A molecular switch is a molecule that can undergo reversible shifts between two stable physical states in response to external stimuli. These include changes in pH, light, temperature, electrical current, or the presence of a ligand.[98] In nature, molecular switches can be found in biochemical processes such as allosteric regulation, whereby a ligand binds onto an allosteric site of an enzyme, causing a conformational change to either enable or disable the enzyme from functioning. Retinal, a polyene chromophore, serves to provide vision to many animals upon photoisomerization in the photoreceptor cells in the retinas of the eyes.[99] Using these properties seen in nature, researchers have employed synthetic strategies to imitate the function of molecular switches in order to visualize biological processes.

One such example in the field of chemical biology is the use of a photochromic molecular switch – an azobenzene substituted naphthyridine carbamate dimer (NCDA)[100] **2.011** (Scheme 2-3). In the cis-form **2.012**, accessed by photoswitching at 360nm, ssDNA that can't hybridize spontaneously because of one GG mismatch in their sequence is hybridized to form the DNA duplex by complexation of the surrounding nucleotides. Given this transformation has been demonstrated to being reversible, this technique is potentially powerful in that DNA engineered to translate into useful markers downstream can be controlled bidirectionally with this motif upon activation/deactivation of NCDA by light. This enables scientists to impart a great degree of control at the molecular level. More on how azobenzenes and other molecular switches have been implicated as photoswitches for biomolecules, cations and anions can be found in several reviews.[101]

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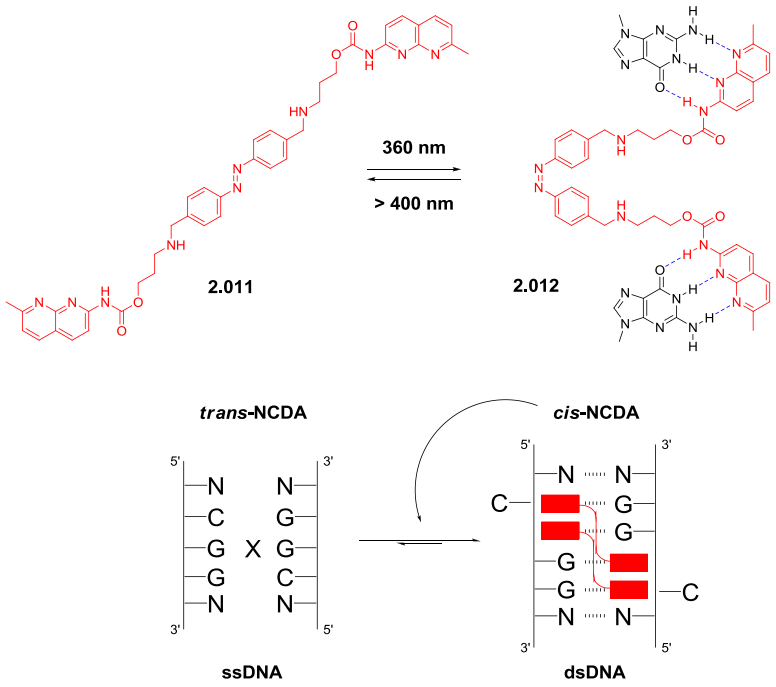
98 "Molecular Machines and Motors (Structure and Bonding)" Sauvage, J-P. (Ed.) Springer: **2010**, 312 pages.

99 von Lintig, J.; Vogt, K. *J. Biol. Chem.* **2000**, *275*, 11915; Bu, Z.

100 Dohno, C.; Uno, S-N.; Nakatani, K. *J. Am. Chem. Soc.* **2007**, *129*, 11898.

101 (a) Beharry, A.A.; Woolley, G.A. *Chem. Soc. Rev.* **2011**, *40*, 4422. (b) Natali, M.; Giordani, S. *Chem. Soc. Rev.* **2012**, *14*, 4010.

Scheme 2-3 Use of azobenzene substituted napththyridine carbamate dimer as a photoswitchable molecular glue for ssDNA



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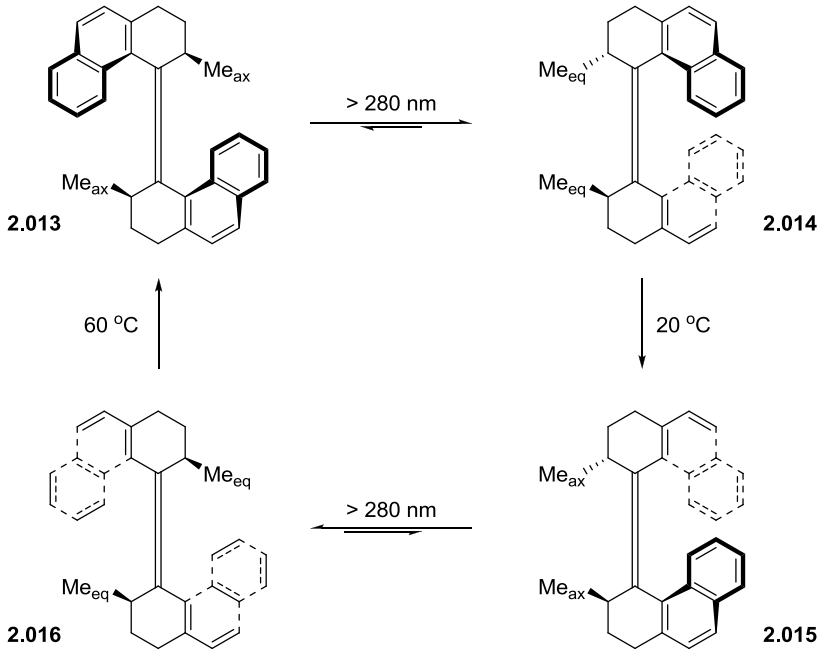
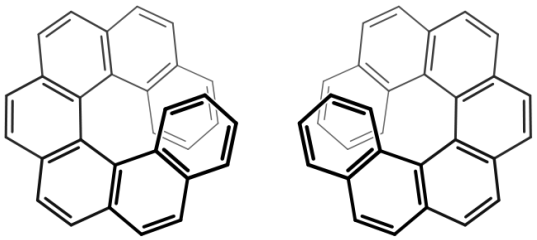
2.1.3 Light Driven Molecular Motors and Switches

In 1999, Feringa and coworkers prepared the first example of a light-driven molecular motor **2.013** (Scheme 2-4). The molecular framework is that of a chiral tetrasubstituted helical alkene, and has received growing interest since its development. These motors are capable of performing perpetual unidirectional 360^{o} motion about the olefin C-C bond upon light irradiation and thermal assistance. The direction of rotary motion is governed by the chirality of the stereogenic center(s) in the helical molecule. Helical chirality is defined by the right or left-handed of the molecule upon curling either hand against the vertical axis, whichever can fit along the contour of the outer chain such that the thumb points up as in the right-hand rule. This is applied biological systems when determining the helicity of an alpha helix in secondary protein structure, among other helical substrates. A *P-helix* is defined is a right-handed helix, and an *M-helix* is a left-handed helix. An example of which is illustrated in the configuration of haptahelicene (Scheme 2-5).

Scheme 2-4 Feringa's first generation optically driven molecular motor



Scheme 2-5 Both *P* and *M* forms of heptahelicene

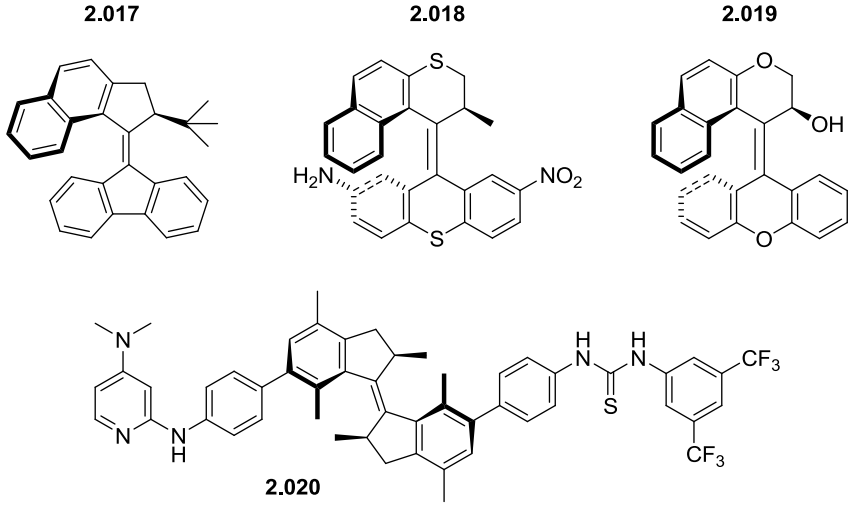


P-helix *M*-helix

In Feringa's system, **2.013** undergoes 4 steps to complete one rotational cycle (Scheme 2-4). This first starts with a low temperature endothermic photoisomerization of the trans-(*P*,*P*)-isomer to the cis-(*M*,*M*)-intermediate **2.014**. During this process the axial methyl groups are converted into the less sterically favourable equatorial groups. Upon warming the unstable intermediate to room temperature, the (*M*,*M*) groups are exothermally converted back to the (*P*,*P*) cis axial groups again **2.015**, and the helix inversion is carried out with the napthyl groups past each other. As the axial isomer is more stable than the equatorial one, reverse rotation is

blocked. **2.015** is subjected to a second photoisomerization and converts to unstable (*M*,*M*)-trans **2.016**. A thermal isomerization process at 60 ^{o}C finishes the cycle, by having the methyl groups climb over the napthyl groups and switch back to their stable axial configurations. The reaction time of this first generation motor is slow, and is not nearly comparable to the rotation speeds encountered by motor proteins in biological systems. Since then, a second generation of molecular motors **2.017** (Scheme 2-6) has been made with a fluorine lower half, to give the fastest system to date, with a thermal helix inversion of 0.005 seconds.[102]

Scheme 2-6 Representative examples of molecular motors and switches with various applications



Other molecules bearing a similar scaffold have been designed for different applications. Feringa's **2.018** and Tietze's **2.019**, have been synthesized as molecular switches[103] with the potential implication in optical data storage. More recently, the Feringa group demonstrated how motor-based asymmetric catalyst[104] **2.020** can be utilized in organocatalysis, which can be modulated by light in situ to generate either enantiomer of the product **2.021** in a thio-1,4 Michael addition with moderate er of 75:25 (Scheme 2-7).

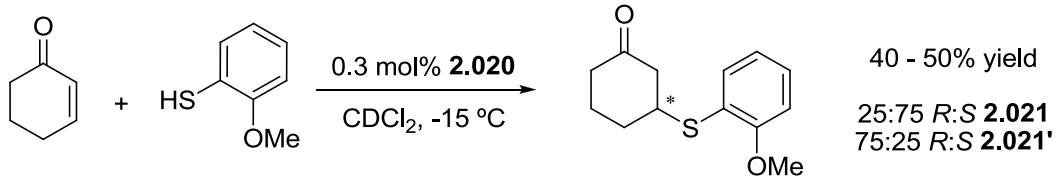
---

[102] Vicario, J.; Walko, M.; Meetsma, A.; Feringa, B.L. *J. Am. Chem. Soc.* **2006**, *128*, 5127.

[103] (a) See ref. 99; Feringa, B.L. *J. Org. Chem.* **2007**, *72*, 6635; Ruangsupapichat, N.; Pollard, M.M.; Feringa B.L. *Nat. Chem.* **2011**, *3*, 53. (b) Tietze, L.F.; Düfert, M.A.; Lotz, F.; Sçlter, L.; Oum, K.; Lenzer, T.; Beck, T.; Herbst-Irmer, R. *J. Am. Chem. Soc.* **2009**, *131*, 17879.

[104] Wang. J; Feringa, B.L. *Science* **2011**, 331, 1429.

Scheme 2-7 Application of molecular motor **2.020** in organocatalysis

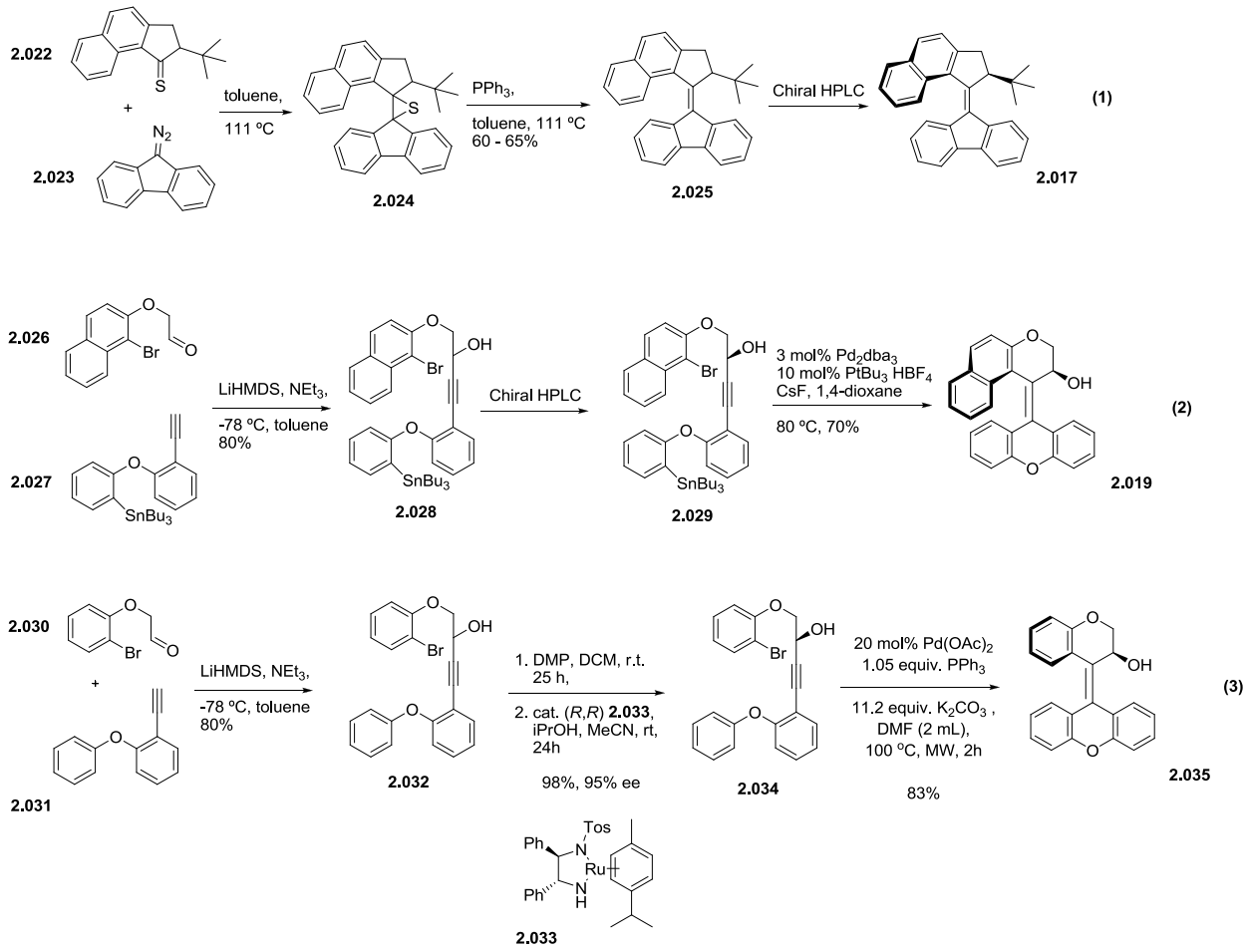


Subtle and distinct structural modifications are generally required for fine-tuning of rotary motion of such artificial molecular devices. To attain this goal, methods for the rapid and modular synthesis of tetrasubstituted helical alkenes are highly desirable.[105] In Feringa's preparation of tetrasubstituted helical alkenes (Scheme 2-8, Eq. 1), the fragments **2.022** and **2.023** are installed together by a Barton-Kellogg reaction, followed by a sulfide elimination to obtain racemic **2.025**, which is then subjected to chiral HPLC to acquire the second generation motor **2.017**. Another contribution to this field has been from Tietze and coworkers' in which they report installing two fragments together (**2.026** and **2.027**) by an alkynyl attack of a pendant aldehyde and resolving the chiral material by HPLC (Scheme 2-8, Eq. 2). They then subject intermediate **2.029** to Stille coupling to construct two C-C bonds in tandem to furnish switch **2.019**. A more recent synthesis by the Tietze group avoids the use of chiral HPLC by effecting an asymmetric reduction of the ketone, after oxidation of **2.032**, using Noyori's hydrogenation catalyst **2.033**, before using a Pd-catalyzed tandem C-H functionalization to construct the helical alkene **2.035** in a domino process (Scheme 2-8, Eq. 3).

---

[105] Jager, W.F.; de Jong, J.C.; de Lange, B.; Huck, N.P.M.; Meetsma, A.; Feringa, B.L. *Angew. Chem. Int. Ed.* **1995**, *107*, 346. For recent work on the synthesis of tetrasubstituted alkenes, see: (a) Gericke, K.M.; Chai, D.I.; Bieler, N.; Lautens, M. *Angew. Chem.* **2009**, *121*, 1475; *Angew. Chem. Int. Ed.* **2009**, *48*, 1447. (b) Tietze, L.F.; Dufert, M.A.; Lotz, F.; Sçlter, L.; Oum, K.; Lenzer, T.; Beck, T.; Herbst-Irmer, R. *J. Am. Chem. Soc*. **2009**, *131*, 17879. (c) Tietze, L.F.; Dufert, M.A.; Hungerland, T.; Oum, K.; Lenzer, T. *Chem. Eur. J.* **2011**, *17*, 8452. (d) Tietze, L.F.; Hungerland, T.; Dufert, M.A.; Objartel, I.; Stalke, D. *Chem. Eur. J.* **2012**, *18*, 3286. (e) Hojo, D.; Noguchi, K.; Tanaka, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 8129. (f) Kwon, K-H.; Lee, D.W.; Yi, C.S. *Angew. Chem. Int. Ed.* **2011**, *50*, 1692. (g) Arthuis, M.; Pontikis, R.; Florent, J-C. *J. Org. Chem.* **2009**, *74*, 2234.

Scheme 2-8 Various synthetic routes of past molecular motors



Our group has previously demonstrated the feasibility of forming tetrasubstituted alkene switch **2.038** by employing a Pd-catalyzed norbornene mediated domino reaction involving multiple C-H functionalizations (Scheme 2-9).[106] This reaction was first established by the Catellani group and later adapted by the Lautens group for this application. The reaction relies on norbornene, which not only acts as a promoter,[107] but becomes incorprorated into the product. We report herein two updates to this chemistry. The first is a highly modular and stereoselective approach to synthesize sterically crowded tetrasubstituted helical alkenes to form chiral molecular motors (Section 2.1). The second is a novel domino reaction to access sterically

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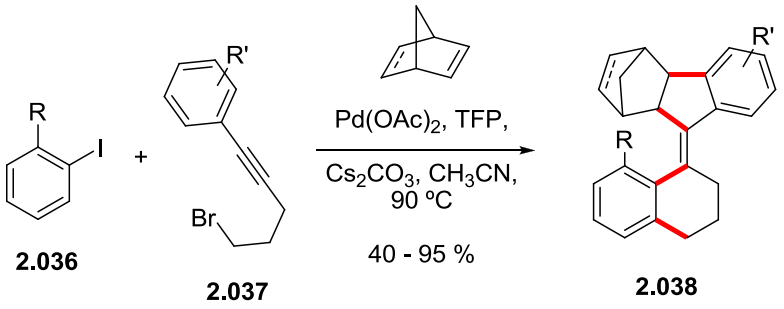
[106] See ref. 102 (b).

[107] (a) Catellani, M. *Top. Organomet. Chem*. **2005**, *14*, 21. (b) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem.* **2010**, *292*, 1.

crowded molecular motors and switches not bearing norbornene, whilst using norbornene to facilitate the reaction (Section 2.2). Both methods are quite attractive in that multiple sequential C-H activations significantly shortens the number of synthetic steps by precluding the requirement of prefunctionalization of either or both coupling partners.

Scheme 2-9 Lautens' group first contribution to the facile formation of molecular switches



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2.2 Construction of Molecular Motors and Switches

2.2.1 Molecular Motors Bearing Norbornene

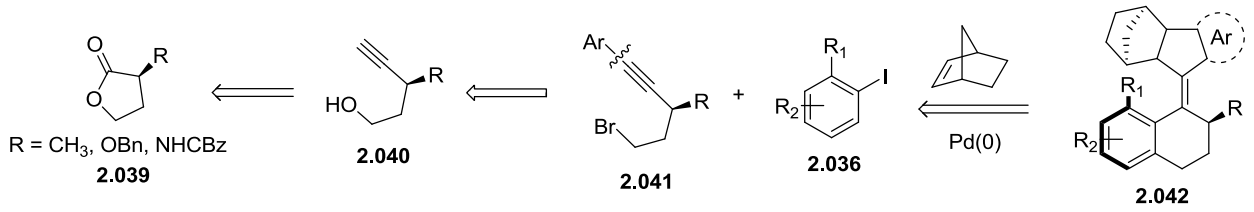
On the basis of our previous synthesis of tetrasubstituted helical alkenes,[108] chiral alkenes **2.042** should be accessible from the commercially available *ortho*-substituted aryl iodides **2.036** and enantiomerically pure bromoalkyl aryl alkynes **2.041** via a palladium-catalyzed, norbornene-mediated domino reaction developed by Catellani and coworkers[109] (Scheme 2-10). This process forms four carbon-carbon bonds in one synthetic sequence. We anticipated that the stereochemistry of the bromide-containing precursor remains intact throughout the reaction sequence. The bromides can be retrosynthetically derived from chiral alkynes **2.040**, which are made from chiral α-substituted lactones **2.039**. Notably, the ease of access to chiral α-lactones offered structural diversity of the helical alkene, as a variety of substituted groups, based on carbon, oxygen, and nitrogen, can be introduced at the stereogenic center.

---

[108] Gericke, K.M.; Chai, D.I.; Bieler, N.; Lautens, M. *Angew. Chem.* **2009**, *121*, 1475; *Angew. Chem. Int. Ed*. **2009**, *48*, 1447.

[109] Catellani, M.; Frignani, F.; Rangoni, A.; *Angew. Chem. Int. Ed.* **1997**, *36*, 119. For a review on norbornene mediated *ortho* C-H functionalization see *Topics in Current Chemistry: C-H Activation*, Vol. *292*, 1-33 (Eds: J-Q. Yu, Z. Shi), Springer: Berlin, **2010**.

Scheme 2-10 Proposed synthesis of chiral tetrasubstituted helical alkenes



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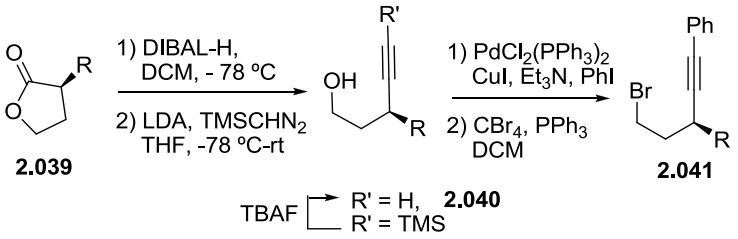
Our synthesis begins with the preparation of optically pure alkynes **2.041**. During the course of the investigation, we compared several synthetic pathways, and the most modular and high yielding method is shown in Table 2-1. Alkynes with various α-substituents (OBn, CH_3, NHCBz) were efficiently synthesized from the corresponding lactones **2.039** via a homologative alkynylation sequence.[110] The corresponding lactone was prepared according to literature procedure.[111] Reduction of the lactones to lactols with diisobutylaluminium hydride (DIBAL) followed by a homologative rearrangement with $TMSCHN_2$ and LDA provided the corresponding alkynes in good yields. Interestingly, the formation of C-silated alkynes was

[110] (a) Myers, A.G.; Goldberg, S.D.; *Angew. Chem., Int. Ed.* **2000**, *29*, 2732. (b) Smith, A.B.; Fox, R.J.; Vanecko, J.A. *Org. Lett.* **2005**, *7*, 3099.

[111] The enantiomerically pure α-lactones were prepared according to literature procedures. See Supporting Information for details.

Table 2-1 Synthesis of enantiomerically pure bromoalkyl aryl alkynes



2.039 **2.040** **2.041**

entry	**2.039** (R-group)	**2.040** yield [%][a]	**2.041** yield [%][a], (*ee*[%][b]),
1	(*S*)-**2.039a** (OBn)	(*S*)-**2.040a** R' = H, 30 %	(*S*)-**2.041a** 1) 80 % 2) 89 % (>99)
2	(*R*)-**2.039a** (OBn)	(*R*)-**2.040a** R' = H, 55 %	(*R*)-**2.041a** 1) 83 2) 86 (>99)
3[c]	(*S*)-**2.039b** (NHCbz)	(*S*)-**2.040b** R' = H, 38 %	(*S*)-**2.041b** 1) 82 2) 93 (98.5)
4[c]	(*R*)-**2.039b** (NHCbz)	(*R*)-**2.040b** R'= H, 41 %	(*R*)-**2.041b** 1) 82 2) 92 (98.5)
5	(*R*)-**2.039c** (CH_3)	(*R*)-**2.040c** R' = H, 51 %	(*R*)-**2.041c** 1) 80 2) 80 (>99)

[a] Yield of isolated products. [b] The *ee* values were determined by chiral HPLC. [c] My contributions. Reprinted (adapted) with permission from ref. 87a. © 2012 American Chemical Society

observed during the rearrangement to **2.040**, which was readily converted to the desired products through TBAF desilation.[112] The required chiral bromoalkyl aryl alkyne **2.041** was readily obtained in high yield with, retaining its enantioselectivity (up to 99% ee), through a modular two-step sequence, including installation of an aryl group via a Sonogashira coupling and conversion of the alcohol to a bromide via an Appel reaction.[113] The corresponding enantiomers of the bromide precursors were prepared from the enantiomers of the chiral lactones through an identical synthetic sequence. The formation of both enantiomers allows for an investigation of the stereochemical outcome of the helical alkene formation, along with the capacity to study their respective rotational path upon irradiation with light.

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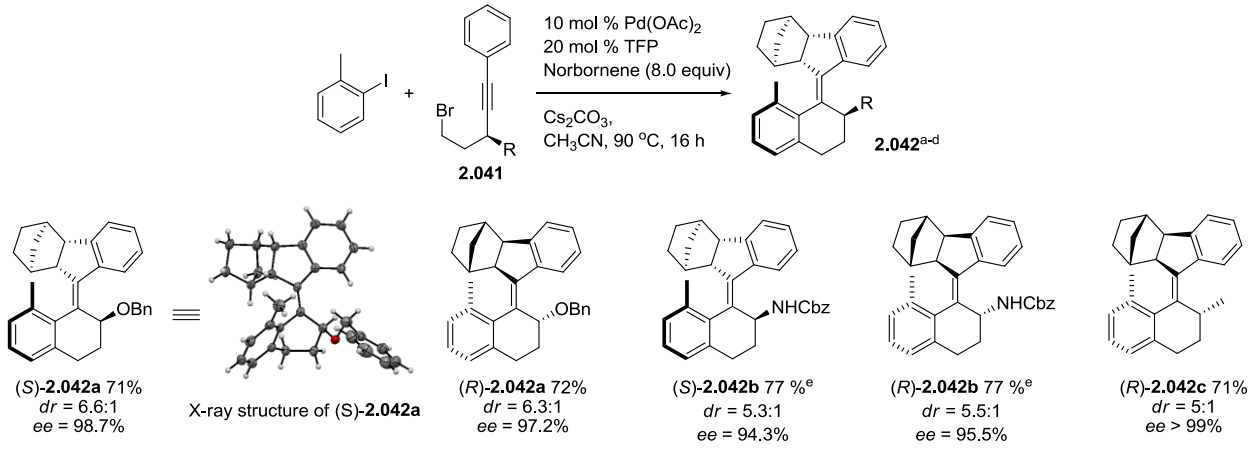
[112] This side product formation was also observed by others. See: Fürstner, A.; Wuchrer, M. *Chem.–Eur. J.*, **2006**, *12*, 76–89.

[113] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 16, 4467. (b) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801. (c) Gericke, K.M., Chai, D.I., Lautens, M. *Tetrahedron* **2008**, *64*, 6002.

With the enantiopure substrates in hand, we examined the domino process between bromide (*S*)-**2.041a** and 2-iodotoluene using the standard condition used in our previous work.[114] The desired tetrasubstituted alkene (*S*)-**2.042a** was formed in 71% yield (Scheme 2-11). Its helical structure and connectivity as well as the absolute stereochemistry were confirmed by X-ray crystal analysis. No significant improvement in yield was observed upon reaction optimization. In the same manner as (*S*)-**2.042a**, the corresponding enantiomer (*R*)-**2.042a** was prepared from the bromide (*R*)-**2.041a** in good yield. The tetrasubstituted alkenes bearing nitrogen [(*S*)-**2.042b** and (*R*)-**2.042b**] and carbon (*R*)-**2.042c** substitutents at the stereogenic center were also obtained in good yield. It is noteworthy that the installation of a nitrogen-substituted group at the stereogenic center has not been demonstrated in previous helical alkene syntheses.[115]

Scheme 2-11 Synthesis of tetrasubstituted alkenes with various substituents at the stereogenic center



[a] Reaction was conducted in 0.2 mmol scale (**(*S*)-2.042a** in 0.4 mmol scale). [b] Yield of isolated products. [c] The *dr* values were determined by ^{1}H-NMR of the crude. [d] The *ee* values were determined by chiral HPLC. [e] My contributions. Reprinted (adapted) with permission from ref. 87a. © 2012 American Chemical Society

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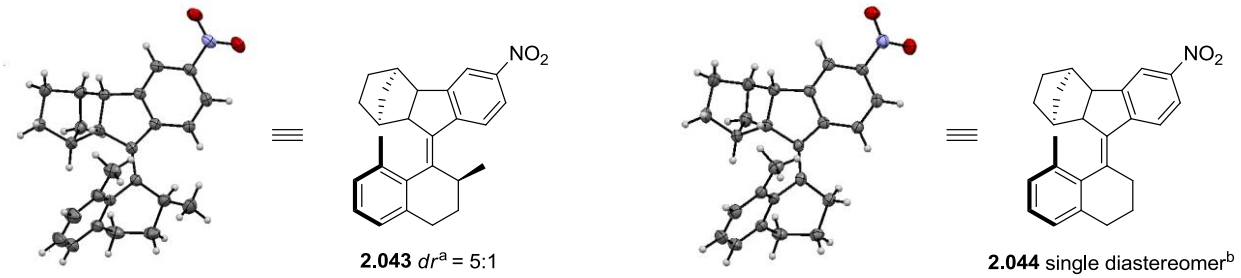
114 Gericke, K.M.; Chai, D.I.; Bieler, N.; Lautens, M. *Angew. Chem.* **2009**, *121*, 1475; *Angew. Chem. Int. Ed*. **2009**, *48*, 1447.

115 See ref. 102

The stereochemical outcome of the domino reaction was analyzed using ^{1}H NMR spectroscopy, HPLC along with X-ray crystallography. The chiral helical alkenes were obtained in excellent enantioselectivity (up to 99% ee) in all cases, suggesting the retention of stereochemistry of the bromide precursors throughout the various bond forming process. We observed moderate diastereoselectivity (5:1 – 6.6:1), yet the formation of a single diastereomer was observed in our previous synthesis of tetrasubstituted alkenes, such as **2.044**[116] (Scheme 2-12).

Scheme 2-12 X-ray crystal structures of **2.043** and **2.044**



[a] **2.043** was synthesized in racemic form and the *dr* value was determined by ^{1}H-NMR of crude product. [b] **2.044** was taken from reference 108. Reprinted (adapted) with permission from ref. 87a. © 2012 American Chemical Society

This indicates that the observed moderate diastereoselectivity is attributed to the presence of the substituent at the propargyl position of the bromide precursors. It appears that incorporation of norbornene in this domino reaction can be a highly stereoselective process with exclusive *exo*-facial selectivity as shown by the two X-ray crystal structures, **2.043** and **2.044**. The origin of the observed diastereoselectivity possibly results from the induced helical chirality upon carbopalladation onto the tethered alkyne (**2.045** to **2.046**), as shown in the proposed reaction mechanism (Scheme 2-13). Interestingly, the induced helical chirality is irrelevant to the nature of the substituent (OBn vs CH_3) as shown in the crystal structure of (*S*)-**2.042a** and **2.043**. We postulate that the helical chirality in the alkene formation is the result of conformational

[116] See ref. 111

preference on the ring containing the exocyclic double bond (**2.046** to **2.047**).[117] Presumably, this induction of helical chirality is driven by the unfavourable 1,3-allylic strain in **2.046** between the pseudoequatorial R group and the phenyl substitutent,[118] which leads to the favourable conformation in **2.047** with R being in the pseudoaxial position. Notably, the induced helical chirality is controlled by the stereogenic center in the bromide starting materials, given that the (*S*)-enantiomer predominantly affords (*P*)-helicity and the (*R*)-enantiomer (*M*)-helicity. These stereochemical control results are consistent with Tietze's work in the synthesis of helical alkenes via an intramolecular domino reaction. It is noteworthy that these tetrasusbtituted alkenes are configurationally stable and E/Z isomerization was not observed.

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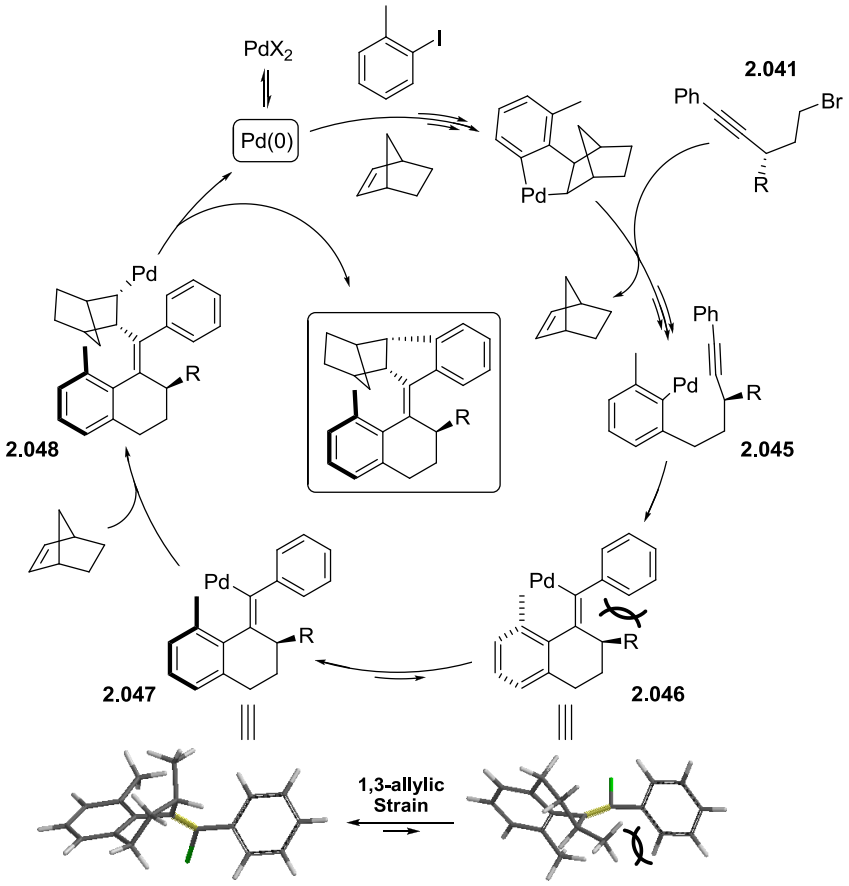
[117] A chelation model between the palladium and hydroxyl substituent during carbopalladation onto the alkyne was proposed to explain the complete diastereoselectivity in the tetra-substituted alkene formation via a domino reaction. See reference 102 (b) and Machotta, A.B.; Straub, B.F.; Oestreich, M. *J. Am. Chem. Soc.* **2007**, *129*, 13455.

[118] For 1,3 allylic strain as a controlling factor in stereoselective transformations, see: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffmann, R.W. *Chem. Rev.* **1989,** *89*, 1841.

Scheme 2-13 Proposed reaction mechanism explaining the stereoselectivity in the domino reaction

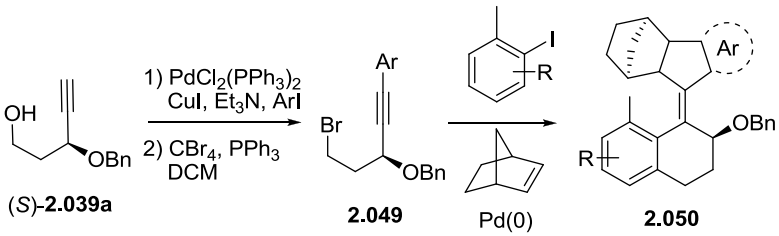


[a] Ligand and solvent molecules omitted for clarity. Only key intermediates are shown. For the detailed mechanism see ref 6a. [b] Modeling on the substrate (*R*)-**2.041c** bearing methyl substituent was performed. Reprinted (adapted) with permission from ref. 87a. © 2012 American Chemical Society

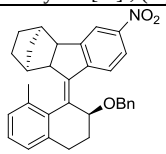
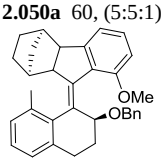
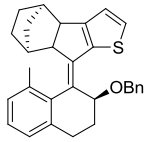
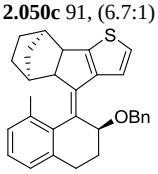
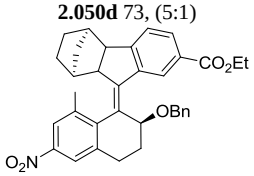
The ease of introducing aryl groups on chiral alkynes through Sonogashira coupling offers a high degree of modularity for the synthesis of chiral helical alkenes (Table 2-2). The bromide precursors bearing an electron-withdrawing group (NO_2, **2.049a**) and an electron-donating group (OMe, **2.049b**) on the aryl moieties afforded **2.050a** and **2.050b** in good yields, respectively. Heterocycles can also be introduced onto the alkyne to give the corresponding bromide precursors (**2.049c** and **2.049d**), which delivered the tetrasubstituted alkene products (**2.050c** and **2.050d**) in good to excellent yield. Interestingly, a single isomer **2.050d** was observed for the 3-thiophene-yl-substituted precursor **2.049d**. This protocol also allows for the synthesis of alkene product **2.050e** bearing a carboxylate group on one aryl ring and a nitro

group on the other, which can be used as handles for further manipulation and incorporation into a larger system.[119]

Table 2-2 Scope of tetrasubstituted alkenes with various aromatic substituents



(*S*)-**2.039a** **2.049** **2.050**

entry	**2.049** yield [%][b]	**2.050** yield [%][b], (dr)[c]
1	Ar = 4-$NO_2C_6H_4$, **2.049a** 1) 81 2) 89	 **2.050a** 60, (5:5:1)
2[e]	Ar = 2-$MeOC_6H_4$, **2.049b** 1) 83 2) 99	 **2.050b** 76, (5.3:1)
3[e]	Ar = 2-thiophene, **2.049c** 1) 84 2) 99	 **2.050c** 91, (6.7:1)
4[e]	Ar = 3-thiophene, **2.049d** 1) 94 2) 99	 **2.050d** 73, (5:1)
5	Ar = 3-$CO_2EtC_6H_4$, **2.049e** 1) 80 2) 91	 **2.050e**[d] 73, (6:1)

[a] The domino reaction was conducted in 0.2 mmol scale using the same reaction conditions as in Scheme 2. [b] Yield of isolated products. [c] The *dr* values were determined by ^{1}H-NMR of the crude. [d] Performed on 1.0 mmol scale. [e] My contributions. Reprinted (adapted) with permission from ref. 87a. © 2012 American Chemical Society

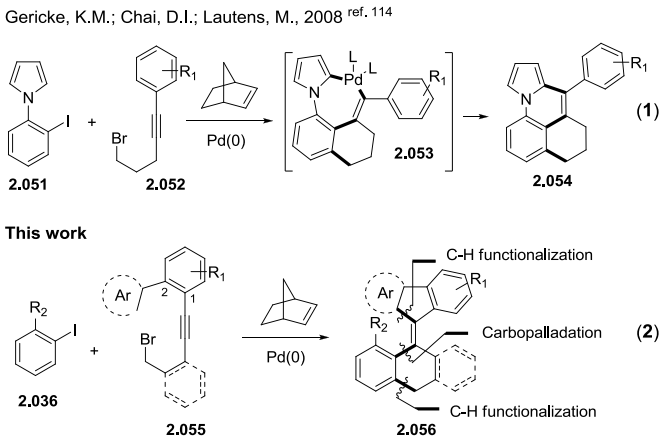
119 (a) van Delden, R.A.; ter Wiel, M.K.J.; Pollard, M.M.; Vicario, J.; Koumura, N.; Feringa, B.L. *Nature* **2005**, *437*, 1337. (b) Eelkema, R.; Pollard, M.M.; Vicario, J.; Katsonis, N.; Ramon, B.S.; Bastiaansen, C.W.M.; Broer, D.J.; Feringa, B.L. *Nature* **2006**, *440*, 163.

This works marks the development of a rapid and highly modular approach to accessing chiral tetrasubstituted helical alkenes by employing a palladium-catalyzed norbornene-mediated domino reaction as the key step. The high structural diversity and excellent stereoselectivity is owed to a very efficient synthesis of a diverse class of enantiopure bromide precursors stemming from chiral lactones. Three characteristic elements of stereoselectivity during the multiple bond formation were observed, and the capacity to form both isomers gives rise to further studies on their photochemical properties as light-driven rotary molecular motors.

2.2.2 Molecular Motors and Switches Lacking Norbornene

Previously we demonstrated the feasibility of forming a variety of tetrasubstituted alkenes (**2.038**, **2.042**, and **2.050)** by a Pd-catalyzed norbornene mediated domino reaction involving multiple C-H functionalizations.[120] We observed that norbornene not only acted as a promoter,[121] but was incorporated into the product. To increase the molecular diversity of these products and to allow for the fine-tuning of their photochemical properties, we discuss a novel[122] domino reaction to access sterically crowded helical alkenes **2.056** (Scheme 2-14, eq. 2) without norbornene incorporation, whilst using norbornene to facilitate the C-H activations.

Scheme 2-14 Work preceding this report and a proposed retrosynthetic analysis



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[120] See ref. 85a, 105.

[121] See ref. 106.

[122] Liu, H.; El-Salfiti, M.; Lautens, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 9846.

Our design was inspired by our previous synthesis of fused tetracyclic pyrroles[123] **2.054** (Scheme 2-14, eq. 1), wherein a norbornene mediated *ortho*-alkylation of an aryl iodide **2.051** followed by carbopalladation of a tethered alkyne **2.052** resulted in a vinylpalladium species **2.053**. This intermediate subsequently underwent an intramolecular C-H functionalization on the pendant pyrrole to afford the desired product. We envisioned that, if the bromoalkyl aryl alkyne precursor **2.052** was appended with a 2-substituted aryl/heterocyclic group on the aromatic ring (**2.055**) (Scheme 2-14, eq. 2), then carbon-carbon bond formation should occur between the vinylpalladium species and the pendant aryl/heterocyclic group by C-H functionalization, thereby providing tetrasubstituted alkenes lacking the norbornene moiety.

To test this approach, we chose a pyrrole moiety as the pendant heterocycle in the bromoalkyl aryl alkyne precursor. The 2-pyrrolyl substituted bromoalkyl aryl alkyne **2.058** can be easily obtained from *ortho*-iodoanilines in a three step synthesis[124] involving a Paal-Knorr pyrrole synthesis. With substrate **2.058** in hand, we examined this domino process using the standard reaction conditions previously used in our earlier work.[125] To our delight, the desired tetrasubstituted alkene **2.059a** was obtained in 31% yield (Scheme 2-15). Interestingly, the product was isolated as a mixture of E/Z isomers. The ratio of both isomers varied over time in $CDCl_3$ solution, when the sample was not protected from light according to ^{1}H-NMR. Presumably, the isomerization could be acid-catalyzed and/or light-driven. Indeed, when using acid-free conditions along with protection from light, the desired product was obtained as a single isomer. In the optimization study we found that upon switching the ligand from TFP to PPh_3, **2.059a** can be isolated in 68% yield.

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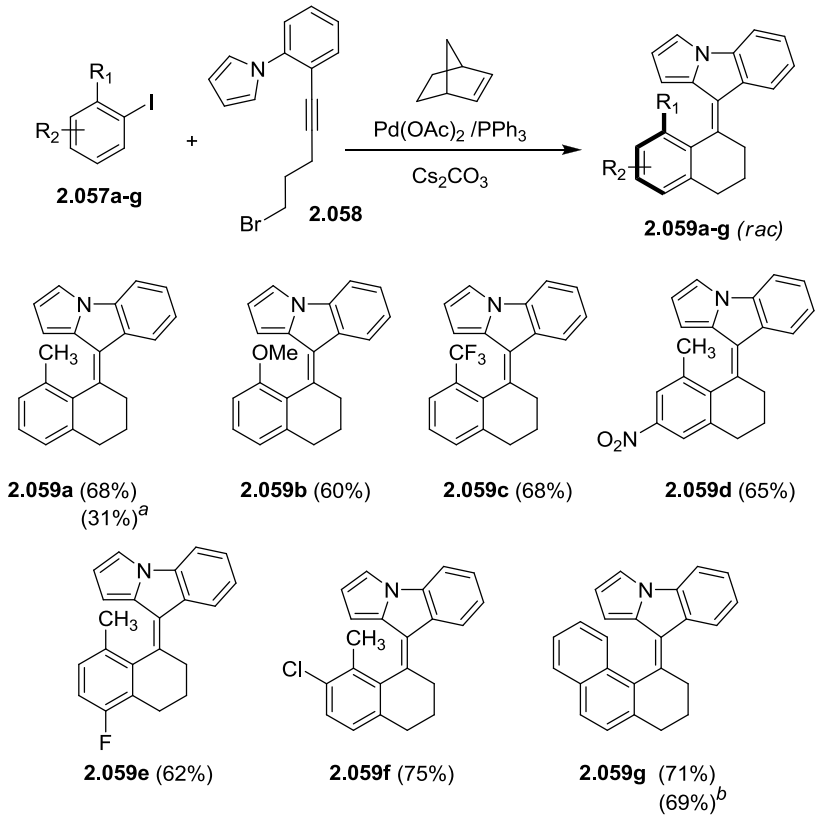
[123] Gericke, K.M.; Chai, D.I.; Lautens, M. *Tetrahedron* **2008**, *64*, 6002.

[124] See supporting information of ref. 119 for more information.

[125] See ref. 102 and Liu, H.; El-Salfiti, M.; Lautens, M. *Org. Lett.* **2012**, *14*, 3648.

Scheme 2-15 Scope of *ortho*-substituted aryl iodides

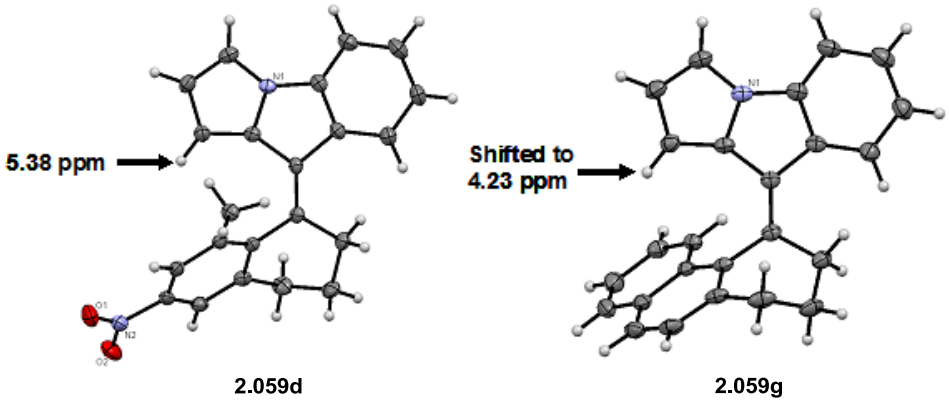


Reagents and reaction conditions: 2-pyrrolyl substituted aryl alkyne **2.058** (ca. 0.2 mmol; 1 equiv), aryl iodide **2.057a-g** (2.0 equiv), norbornene (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (3.0 equiv), acetonitrile (2.0 mL), 90 ^oC, 24h, sealed tube. Isolated yields. [a] Earlier conditions: as described using TFP as ligand in place of PPh_3 and using 3 equiv norbornene. [b] Using 1.0 mmol of **2.058**. Reprinted (adapted) with permission from ref. 87b. © 2012 John Wiley & Sons, Inc.

We then investigated the scope of the reaction using various *ortho*-substituted aryl iodies (Scheme 2-15). Both aryl iodides bearing electron-donating (OMe, **2.057b**) and electron-withdrawing (CF_3, **2.057c**) substitution in the *ortho*-position afforded the corresponding products (**2.059b** and **2.059c**) in good yields, respectively. Aryl iodides containing both an *ortho*-methyl group and either a *para*-nitro (**2.057d**), *meta*-chloro (**2.057e**), or *meta*-fluoro (**2.057f**) substituent gave the corresponding products (**2.059d-f**) in good yields. More importantly, the tolerance of nitro or chloro substituents in the final product allows for further manipulation and is suitable for

incorporation into a larger system.[126] Notably, the helical alkene **2.059g**, which bears a naphthalene substituent, can be prepared in good yield from 1-iodonapthalene **2.057g**. The X-ray crystal structures of **2.059d** and **2.059g** confirm the connectivity and relative configuration of the tetrasubstituted alkenes (Scheme 2-16). The helical structure of **2.059g** was also unambiguously confirmed by ^{1}H NMR spectroscopy. The chemical shift of one of the protons in the pyrrole ring is shifted significantly upfield compared to the corresponding proton in **2.059d** (4.23 ppm vs. 5.38 ppm). Presumably, this is due to a shielding effect by the ring current of the aromatic naphthalene moiety, as suggested by the crystal structure of **2.059g**. The reaction can also be performed on a preparatively useful scale (1 mmol), resulting in a similar yield and affording more than 200 mg of material.

Scheme 2-16 X-ray crystal structures of **2.059d** and **2.059g**



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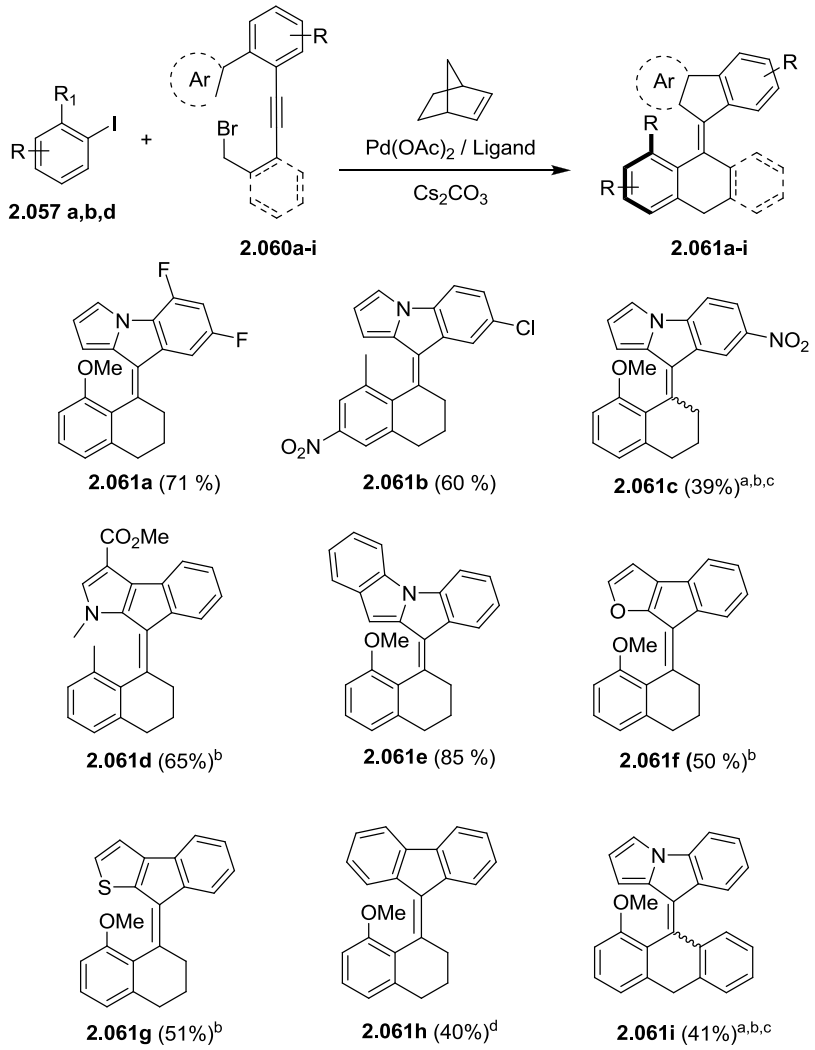
[126] See ref. 116

Scheme 2-17 Scope of bromoalkyl aryl alkynes

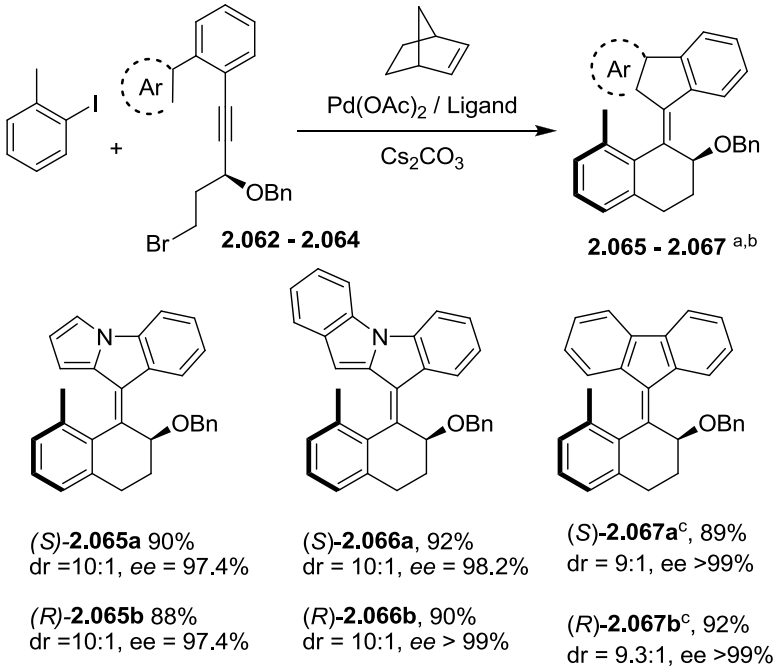


Reagents and reaction conditions: bromoalkyl aryl alkynes **2.060a-i** (ca. 0.2 mmol, 1 equiv), aryl iodide **2.057a**,**b**,**d** (2.0 equiv), norbornene (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (3.0 equiv), acetonitrile (2.0 mL), 90 ^oC, 24 h, sealed tube. Isolated yields. [a] Product was isolated as an *E/Z* mixture (1:1). [b] Using TFP as ligand. [c] My contributions. [d] Using TFP ligand at 120 ^oC. Reprinted (adapted) with permission from ref. 87b. © 2012 John Wiley & Sons, Inc.

The reaction scope was further investigated using bromoalkyl aryl alkynes **2.060a-i** (Scheme 2-17), Which were easily accessibly in a similar manner to **2.059**. A variety of substituents (F, Cl, NO_2) at different positions on the aryl ring of the alkyne system were tolerated, producing the corresponding products **2.061a-c** in moderate to good yields. **2.061c** was isolated as a mixture of E/Z isomers (1:1) despite all efforts to prevent the acid catalyzed isomerization. Presumably, this compound undergoes fast isomerization upon exposure to visible

light. Substrate **2.060d**, which bears a different substituted 2-pyrrolyl moiety, afforded product **2.061d** in good yield. This reaction also tolerated pendant heterocycles other than pyrrole; C-H activation was successful on indole, furan, and thiophene systems to form products **2.061e-g**, respectively, in moderate to good yields. Interestingly, single isomers were observed for furyl and thienyl substituted compounds (**2.061f** and **2.061g**) respectively; unlike their pyrrole based counterparts, these compounds were not sensitive to acid. We also observed that nonheterocyclic nucleophile **2.060h** can be used to give **2.061h** in moderate yield. The reaction scope can be further extended to form crowded helical alkene **2.061i** with four aromatic substituents, which was found to be very sensitive to light when found in solution.[127]

Scheme 2-18 Stereoselective synthesis of tetrasubstituted alkenes



Reagents and reaction conditions: bromoalkyl aryl alkynes **2.062 – 2.064** (ca. 0.2 mmol, 1 equiv), aryl iodide (2.0 equiv), norbornene (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Cs_2CO_3 (3.0 equiv), acetonitrile (2.0 mL), 90 ^oC, 24 h, sealed tube. Isolated yields. [a] *dr* determined by ^1H-NMR of crude product. [b] *ee* determined by chiral HPLC. [c] Using TFP ligand at 120 ^oC. Reprinted (adapted) with permission from ref. 87b. © 2012 John Wiley & Sons, Inc.

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[127] **2.061i** was isolated as a mixture of *E/Z* isomers due to the rapid isomerisation process under visible light. The CD_2Cl_2 solution of **2.061i** changed colour and decomposed at room temperature after one day under visible light as confirmed by ^1H-NMR of the solution.

This method also provides quick access to chiral and enantiomerically enriched tetrasubstituted helical alkenes, (**2.065** – **2.067**) which possess a stereogenic center next to the olefin (Scheme 2-18). It is noteworthy that, as shown by Feringa, the absolute stereochemistry in these alkenes can dictate the direction of molecular rotation upon irradiation.[128] Utilizing the optically pure bromoalkyl aryl alkynes **2.062** – **2.064**, the domino reaction with 2-iododtoluene afforded the corresponding enantiomerically pure precursors, which allows for the study of their distinct rotational behavior upon irradiation. These reactions proceed with retention of stereochemistry of the bromide precursors in excellent enantioselectivity (up to 99% ee). The induction of helical chirality in this multiple bond forming process was observed, as was suggested by the moderate diastereoselectivity of the reaction. Our recent[129] stereoselective synthesis of tetrasubstituted alkenes bearing norbornene also bore the observed helical chirality, in accordance with these findings.

The proposed mechanism of the domino reaction is outlined in Scheme 2-19. Similar to the other norbornene mediated C-H functionalizion processes,[130] a series of reactions involving oxidative addition of the aryl iodide, carbopalladation of norbornene, and electronic metalation followed by deprotonation gives palladacycle **2.069**. Oxidative addition of a bromoalkyl aryl alkyne leads to **2.070**, and rapid reductive elimination delivers *ortho*-alkylated intermediate **2.071**. Because of increased steric demand, a retrocarbopalladation of norbornene then occurs, leading to arylpalladium species **2.072**. Next, intramolecular carbopalladation on the tethered alkyne generates the vinylpalladium species **2.073**. At this point the intermediate can directly induce C-H functionalization on the adjacent pyrrole ring to form **2.074**, and subsequent reductive elimination generates the desired product **2.075**. Because of the high reactivity associated with norbornene (strain energy = 21.6 kcal/mol)[131] and its presence in large excess, the vinyl palladium species **2.073** could undergo intermolecular carbopalladation of norbornene, thus leading to complex **2.076**, to which another C-H functionalization on the adjacent aromatic ring could occur to liberate tetrasubstituted alkene **2.077**. However, this reaction pathway is not

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[128] Jager, W.F.; de Jong, J.C.; de Lange, B.; Huck, N.P.M.; Meetsma, A.; Feringa, B.L. *Angew. Chem.* **1995**, *107*, 346.

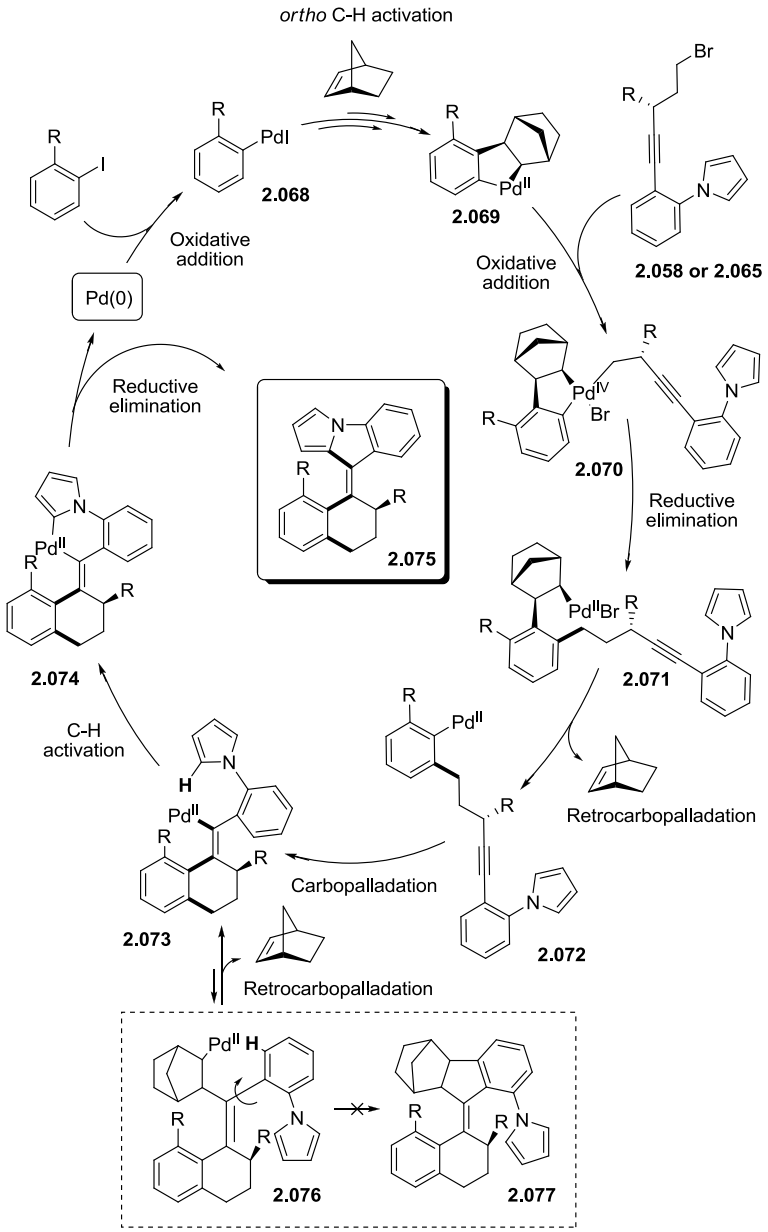
[129] Liu, H.; El-Salfiti, M.; Lautens, M. *Org. Lett.* **2012**, *14*, 3648.

[130] See ref. 104.

[131] Khoury, P.R.; Goddard, J.D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103.

followed, as revealed by the formation of product **2.075**. Presumably, the C-H functionalization of **2.073** to provide **2.074** is much faster than the carbopalladation of norbornene, thereby preventing the formation of **2.076**. Another potential explanation could be the increased steric congestion in complex **2.076**, which would result from the bulky 2-substituted aryl/heterocyclic group. If formed, this species, particularly for **2.062** – **2.064** containing a pendant stereogenic center, would favour the retrocarbopalladation of norbornene to produce **2.073**, despite the use of a large excess of norbornene. Even when a large excess of norbornene (8.0 equivalents) was used, **2.075** was still formed in 55% yield (NMR), suggesting that the norbornene incorporation pathway is less favourable than the directed C-H functionalization. Perhaps this is due to the pyrrole, which disfavours species **2.076**.

Scheme 2-19 Plausible reaction mechanism for the domino process



Ligand and solvent molecules omitted for clarity. Reprinted (adapted) with permission from ref. 87b. © 2012 John Wiley & Sons, Inc.

In summary, a highly efficient and modular synthesis of sterically crowded tetrasubstituted helical alkenes possessing high structural diversity is described. This reaction uses a well established palladium-catalyzed norbornene mediated cascade of C-H activations. The novelty is in the broader access to molecules not bearing norbornene, allowing for potentially broader photochemical behavior upon screening, and this is currently underway.

Experimental Information

General Considerations

General Experimental Procedures: Unless otherwise stated, reactions were carried out under argon atmosphere in sealed tubes (5.0 mL volume with a crimped aluminum lid housing a Teflon septa provided by Biotage) with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel canula. Organic solutions were concentrated by rotary evaporation at 23–40 °C under 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was carried out on pre-coated SIL G/UV254 (0.2 mm) plates from EMD Chemicals. Visualization was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, anisaldehyde or in potassium permanganate ($KMnO_4$), followed by heating using a heat gun. Purification of reaction products were generally done by flash chromatography with Silicycle™ Ultra-Pure 230–400 mesh silica gel, as described by Still and coworkers.[132]

Materials: Acetonitrile was distilled under nitrogen from CaH_2 immediately prior to use. All reagents and metal catalysts were purchased from Sigma-Aldrich, Lancaster, Alfa Aesar or Strem Chemical Company and used without further purification unless otherwise noted. Bromoalkyl aryl alkynes were synthesized according to a literature procedure in a two-step Sonogashira/Appel reaction sequence.[133]

Instrumentation: Melting points were recorded using a Fisher–Johns melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at room temperature using a Varian Gemini-300, Unity-400 or Mercury 400 spectrometer. ^1H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and ^{13}C spectra were referenced to solvent (77.23 ppm for $CDCl_3$ and 54.0 ppm for CD_2Cl_2). No special notation is used for equivalent carbons. IR spectra

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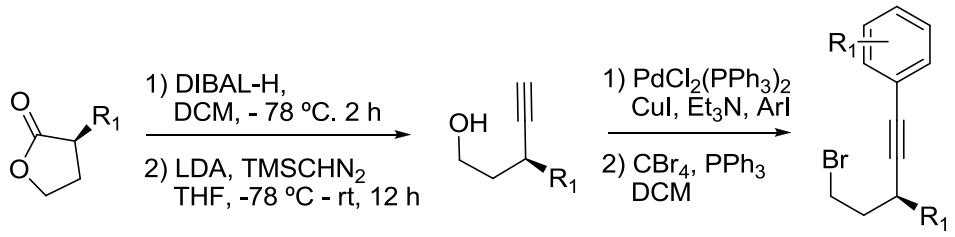
[132] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[133] Gericke, K.M.; Chai, D.I.; Lautens, M. *Tetrahedron*. **2008**, *64*, 6002.

were obtained using a Shimadzu spectrometer in $CHCl_3$ as thin films on NaCl plates. High resolution mass spectra were obtained using a VG 70-250S (double focusing) mass spectrometer at 70 eV unless otherwise noted.

Section 2.1

Synthesis of optically pure bromoalkyl aryl alkynes



General procedure for the homologative alkynylation reaction:

Step 1: The chiral lactone (1 mmol) was dissolved in CH_2Cl_2 (2 mL), cooled to -78°C under argon, and treated dropwise with a solution of diisobutylaluminium hybride in hexanes (1.3 equiv). The reaction mixture was stirred at -78°C for 1 h, quenched cautiously with a saturated solution of Rochelle's salt (~ 1 mL), and stirred for 5 h while slowly being warmed to room temperature. The separated aqueous layer was extracted with ether and the combined organic phases were washed with a small amount of brine, dried and concentrated to give the lactol product, which was used for next step without further purification.

Step 2: *n*-BuLi (2.6 mmol, 2.6 equiv related to the lactol starting material) was slowly added to a solution of $(i\text{Pr})_2\text{NH}$ (2.6 mmol, 2.6 equiv) in THF (6 mL) at -78°C and the resulting mixture was stirred for 10 min, and then for 30 min at room temperature. The freshly prepared LDA solution was cooled to -78°C and a solution of $TMSCHN_2$ (1.2 mmol, 1.2 equiv) was introduced. After stirring for another 1 h at -78°C, a solution of the lactol (1.0 mmol) in THF (4 mL) was added. The resulting mixture was allowed to warm to ambient temperature and stirred overnight (the release of nitrogen was observed upon warming, so care should be taken to have adequate ventilation). The reaction was then quenched with sat. aq. NH_4Cl solution. A standard work up

with ether followed by flash chromatography (Hexanes/EtOAc, 6/1 to 4/1) of the crude product affords the desired alkyne and the corresponding *C*-silyated alkyne.

To convert the side product to the desired product, TBAF (1.3 equiv) was added to a THF solution of the silylated alkyne. After stirring 10 min at room temperature, the reaction mixture was diluted in ether, and washed with sat.NH_4Cl. Repeated extraction of the aqueous phase with ether, drying of the combined organic layers (Na_2SO_4), evaporation of the solvent and flash chromatography as described above afforded a second crop of the desired alkyne.

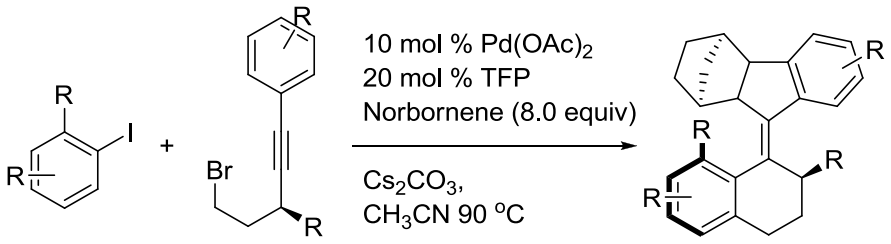
General procedure for Sonogashira coupling:

To the corresponding aryl iodides (1.0 equiv) in Et_3N (5 mL/mmol) were added subsequently $PdCl_2(PPh_3)_2$ (5 mol %), CuI (1.2–5 mol %) and the appropriate alkyne (1.2 equiv) at 25 °C. Stirring was continued for 16 h at 25 °C. The reaction mixture was treated with satd NH_4Cl solution and the resulting mixture was extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and concentration of the appropriate fractions *in vacuo* afforded the desired compounds.

General procedure for the synthesis of bromides via Appel reaction:

To the corresponding alcohols (1.0 equiv) and CBr_4 (1.2 equiv) in CH_2Cl_2 (3–5 mL/mmol) was added PPh_3 (1.2 equiv) in small portions. The reaction mixture was allowed to warm up to 25 °C and stirring was continued until reaction is completed as indicated by TLC. The solvent was then removed in *vacuo*, and the crude product was purified by silica gel flash chromatography, and concentration of the appropriate fractions *in vacuo* afforded the desired compounds.

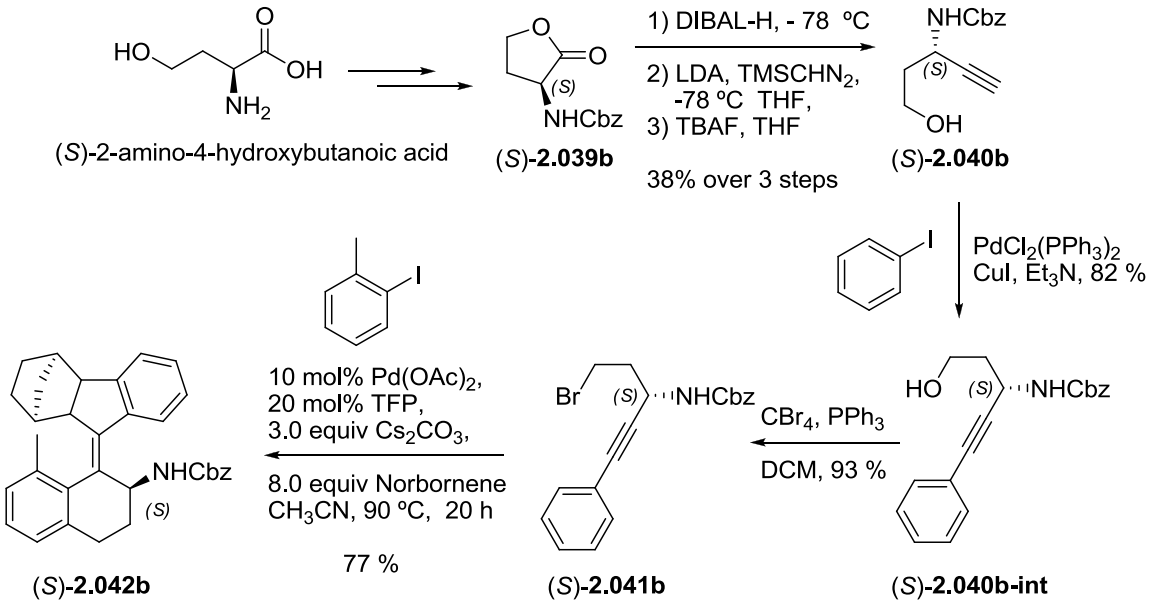
Synthesis of tetrasubstituted helical alkenes



General procedure:

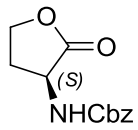
To a 10 mL microwave vessel with a magnetic stir bar were added $Pd(OAc)_2$ (4.50 mg, 10 mol%, 0.02 mmol), TFP (20 mol%, 0.04 mmol), Cs_2CO_3 (0.6 equiv, 195.5mg, 0.6 mmol), bromide precursor (0.2 mmol), aryl iodide (0.4 mmol), norbornene (8.0 equiv). The solvent (CH_3CN, 2 mL) was then added. The tube was flushed with argon for 5 min and sealed. The reaction was stirred at 90 °C for 16 h and then cooled to r.t., diluted with CH_2Cl_2 (4 mL) and filtered through a pad of celite. The filtrate was concentrated to yield the crude product. Purification by flash silica chromatography gave the pure product.

Carbamate protected chiral tetrasubstituted helical alkenes[134]



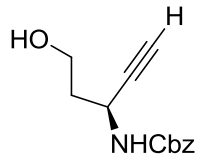
[134] Cyclic (*S*)-**2.039b** was prepared according to literature procedure: Lall, M.S.; Karvellas, C.; Vederas, J.C. *Org. Lett.* **1999**, *1*, 803.

(S)-benzyl 2-oxotetrahydrofuran-3-ylcarbamate (*S*)-**2.039b**



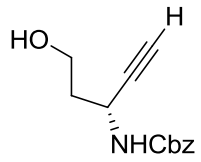
This known compound was prepared according to literature procedure as a white crystalline solid (89 % yield). **m.p.** 121–123 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (m, 5H), 5.35 (br s, 1H), 5.13 (s, 2H), 4.43 (m, 2H), 4.25 (m, 1H), 2.79 (m, 1H), 2.21 (dddd, *J* = 12.0, 11.7, 11.7, 9.0 Hz, 1H); **HRMS** (ESI) Calculated [M+Na^+] $C_{12}H_{13}NNaO_4$: 258.0736, Found: 258.0736. Characterization is in agreement with literature values.

(S)-benzyl 5-hydroxypent-1-yn-3-ylcarbamate (*S*)-**2.040b**



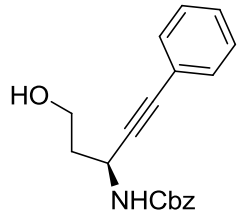
This compound was obtained according to the general procedure for alkyne synthesis. The crude product was purified by flash chromatography on silica gel to afford the desire product as a white gummy oil (38 % yield). **^{1}H NMR** ($CDCl_3$ 400 MHz): δ 7.32 (m, 5H), 5.83 (br d, *J* = 8.1 Hz, 1H), 5.09 (s, 2H), 4.67 (m, 1H), 3.77 (m, 2H), 2.32 (d, *J* = 2.3 Hz, 1H), 2.13 (s, 1H), 1.95 (m, 1H), 1.82 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 136.0, 128.4, 128.1, 128.0, 82.5, 71.7, 67.0, 58.6, 40.8, 38.0; **IR ν_{max}** ($CHCl_3$, cast): 3392, 3291, 2958, 2889, 1679, 1532, 1454, 1256, 1056, 739 cm^{-1}; **HRMS** (ESI) Calculated [M+Na^+] $C_{13}H_{15}NNaO_3$: 256.0944, Found: 256.0947.

(R)-benzyl 5-hydroxypent-1-yn-3-ylcarbamate (*R*)-**2.040b**



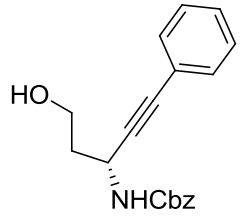
This compound was obtained from D-homoserine in the same manner to (*S*)-**2.040b**. The homologative akynylation gave the desired product as white gummy oil (41%). NMR data is consistent with the corresponding enantiomer (*S*)-**2.040b**.

(S)-benzyl 5-hydroxy-1-phenylpent-1-yn-3-ylcarbamate (*S*)-**2.040b-int**



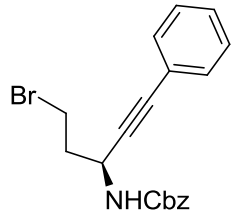
This compound was obtained according to the general procedure for sonogashira coupling. The crude product was purified to give the desire product as a light yellow solid; 82 % yield. **m.p.** 66–68 ^{o}C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (m, 10H), 5.63 (d, *J* = 8.5 Hz, 1H), 5.11 (s, 2H), 4.91 (m, 1H), 3.79 (m, 2H), 2.97 (br s, 1H), 2.04 (m, 1H), 1.88 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.1, 136.1, 131.2, 128.4, 128.3, 128.2, 128.1, 128.0, 122.3, 87.7, 83.5, 67.0, 58.8, 41.4, 38.6; **IR ν_{max}** 3316, 3063, 2956, 1695, 1532, 1338, 1253, 1054, 757; **HRMS** (ESI) Calculated [$M+H^+$] $C_{19}H_{20}NO_3$: 310.1437, Found: 310.1443.

(R)-benzyl 5-hydroxy-1-phenylpent-1-yn-3-ylcarbamate (*R*)-**2.040b-int**



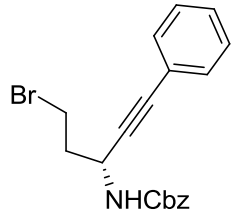
This compound was obtained from (*S*)-**2.040b-int** according to the general procedure for sonogashira coupling (82% yield)**.** NMR data is consistent with the corresponding enantiomer (*S*)-**2.040b-int**.

(S)-benzyl 5-bromo-1-phenylpent-1-yn-3-ylcarbamate (*S*)-**2.041b**



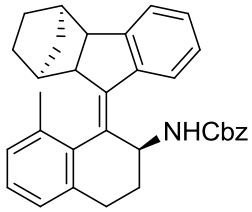
The title compound was prepared according to the general procedure for Appel reaction as a light yellow solid (93 % yield). **m.p.** 71–73 ^{o}C; **[α]$_D^{28}$** +18.3^{o} (*c* 1.15, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (m, 10H), 5.13 (m, 3H), 4.91 (br q, *J* = 14.0, 6.8 Hz, 1H), 3.52 (t, *J* = 7.0 Hz, 2H), 2.31 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.3, 136.0, 131.6, 128.5, 128.4, 128.2, 128.1, 128.1, 122.0, 86.5, 84.2, 67.0, 43.1, 38.8, 28.4; **IR ν_{max}** 3406, 3314, 3033, 2963, 1695, 1530, 1299, 1260, 1243, 1040, 756; **HRMS** (ESI) Calculated [M+H^{+}] $C_{19}H_{19}BrNO_2$: 372.0593, Found: 372.0600. **HPLC analysis** (Chiracel ADH, 2.5% iPrOH/Hexane, 1.00 mL/min, 280 nm); 98.5% *ee*, t_R = 27.6 min.

(R)-benzyl 5-bromo-1-phenylpent-1-yn-3-ylcarbamate (*R*)-**2.041b**



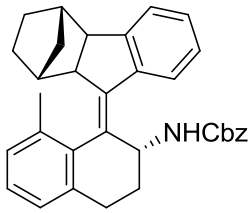
The title compound was prepared according to the general procedure for Appel reaction as a light yellow solid (92 % yield). **[α]$_D^{28}$** -16.5^{o} (*c* 1.15, CHCl3); NMR data are consistent with the corresponding enantiomer (*S*)-**2.041b**; **HPLC analysis** (Chiracel ADH, 2.5% iPrOH/Hexane, 1.00 mL/min, 280 nm); 98.5% *ee*, t_R = 33.3 min.

Tetrasubstituted alkene (*S*)-**2.042b**



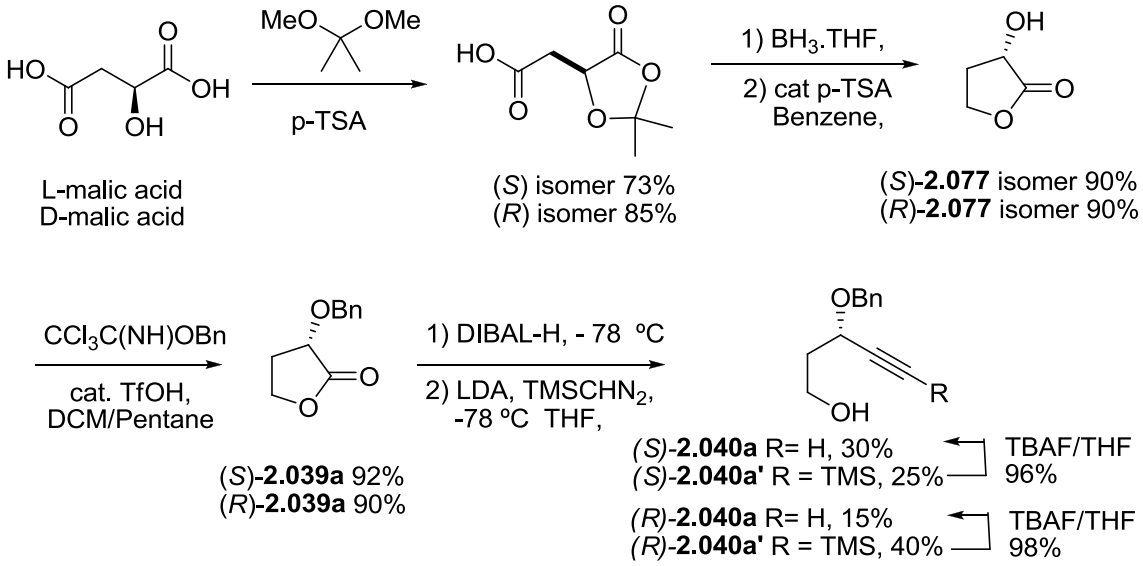
This compound was prepared according to the general procedure for tetrasubstituted alkene synthesis (0.2 mmol scale) as a tan solid in 77 % yield, dr = 5.3:1. **m.p.** 107–108 ^{o}C; **$[\alpha]_D^{28}$** -98.2^{o} (*c* 0.34, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.32 (m, 8H), 7.13 (m, 2H), 7.00 (m, 1H), 5.66 (m, 1H), 5.10 (s, 2H), 4.69 (m, 1H), 2.98 (d, *J* = 7.5 Hz, 1H), 2.84 (d, *J* = 7.5 Hz, 1H), 2.75 (br s, 1H), 2.53 (m, 1H), 2.42 (m, 1H), 2.36 (s, 3H), 2.27 (m, 1H), 1.46 (m, 1H), 1.32 (m, 3H), 1.16 (m, 1H), 0.96 (m, 1H), 0.82 (m, 1H), 0.72 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.7, 150.8, 146.3, 141.5, 138.9, 136.5, 134.7, 128.7, 128.5, 128.5, 128.1, 127.5, 127.0, 125.3, 124.8, 123.6, 66.6, 52.5, 52.0, 51.4, 50.0, 43.3, 40.6, 36.6, 33.1, 32.4, 29.0, 28.4, 28.1, 26.2, 25.1, 20.5, 19.5; **IR ν_{max}** 3435, 3345, 2948, 2869, 1695, 1496, 1471, 1326, 1246, 1050, 909, 774, 736, 697; **HRMS** (ESI) Calculated [$M+H^+$] $C_{33}H_{34}NO_2$: 476.2584, Found: 476.2568 **HPLC analysis** (Chiracel ODH, 1% iPrOH/Hexane, 1.00 mL/min, 210 nm); > 94.3% *ee*, t_R = 5.08 min.

Tetrasubstituted alkene (*R*)-**2.042b**

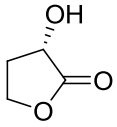


This compound was obtained as a tan solid in 77 % yield, dr = 5:1. **$[\alpha]_D^{28}$** +92.8^{o} (c 0.25, $CHCl_3$); NMR data are consistent with the corresponding enantiomer (*S*)-**2.042b**; **HPLC analysis** (Chiracel ODH, 1% iPrOH/Hexane, 1.00 mL/min, 210 nm); > 95.5% *ee*, t_R = 6.73 min.

O-Benzyl protected chiral tetrasubstituted helical alkenes[135]



(S)-3-hydroxydihydrofuran-2(3H)-one (S)-**2.077**



The crude compound was purified by flash column chromatography (EtOAC/Hexanes 1/1 to 7/3) to afford desired product as a colorless oil (8.22g, 66% over 3 steps); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.51 (ddd, *J* = 10.1, 8.3, 4.0 Hz, 1H), 4.45 (ddd, *J* = 9.0, 2.0 Hz, 1H), 4.24 (ddd, *J* = 10.5, 9.3, 6.0, 1H), 3.12 (br, s, 1H, HO) 2.59 (dddd, *J* = 14.5, 8.0, 6.0, 2.0 Hz, 1H), 2.27 (dddd, *J* = 12.7, 10.5, 10.3, 8.7 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 178.0, 67.7, 65.3, 31.1; The data is consistent with that reported in literature.

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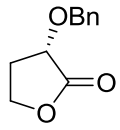
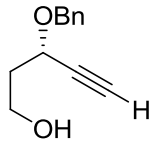
[135] lactone **2.077** was prepared according to literature procedure: Denmark, S.E.; Yang, S-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432. O-Benzyl protected lactone **2.039** was prepared according to literature: Bandur, N.G.; Bruckner D.; Hoffmann, R.W.; Koert, U. *Org. Lett.* **2006**, *8*, 3829. My contribution was the synthesis of (*S*)-**2.040a** from L-malic acid.

(S)-3-(benzyloxy)dihydrofuran-2(3H)-one (S)-**2.039a**



The crude compound was purified by flash column on silica (EtOAC/Hexanes 1/6 to 1/3) to afford desired product as a colorless oil (14.17g, 92%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.50 – 7.31 (m, 5H), 4.91 (d, *J* = 12 Hz, 1H), 4.74 (d, *J* = 12 Hz, 1H), 4.41 (ddd, *J* = 9.1, 8.1, 4.2 Hz, 1H), 4.21 (ddd, *J* = 9.1, 8.1, 4.2 Hz, 1H), 4.17 (t, *J* = 7.9 Hz), 2.45 (dddd, *J* = 13.0, 7.9, 4.2, 4.5 Hz, 1H), 2.28 (qd, *J* = 13.0, 7.9 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ175.4, 137.1, 128.8, 128.5, 128.2, 72.7, 72.4, 65.8, 30.1; The data is consistent with that reported in literature.

(S)-3-(benzyloxy)pent-4-yn-1-ol (S)-**2.040a**



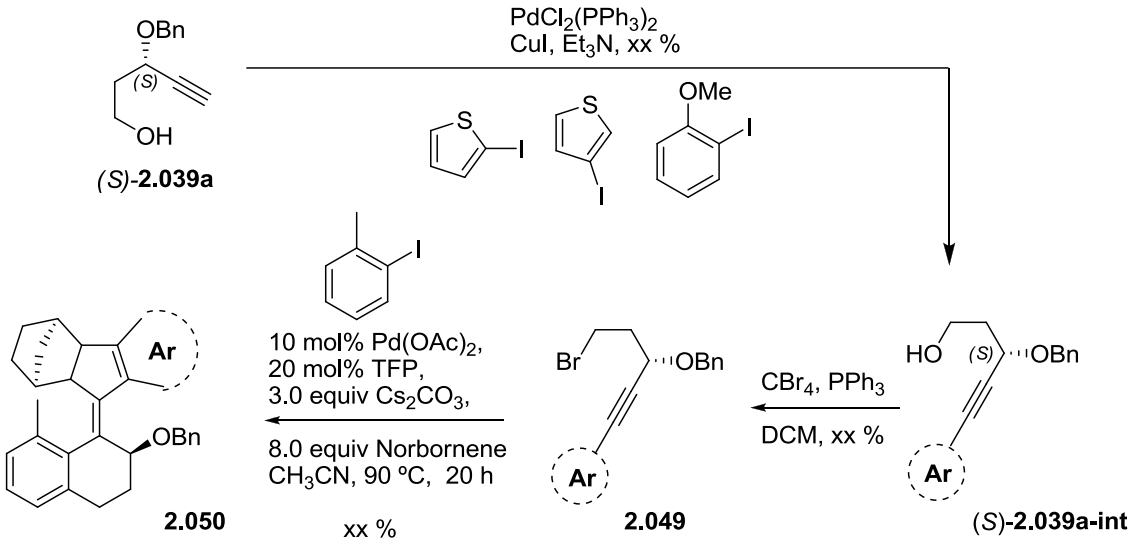
The title compound was prepared according to the general procedure for homologative akynylation reaction. The crude compound was purified by a flash column (EtOAc: Hexane 1:4) to afford the chiral alkye *(S)*-**2.040a** as a light yellow oil (3.0g, 30 %) and the *C*-silylated alkyne *(S)*-**2.040a'** as orange oil (4.5g, 25%). To convert the isolated side product to the desired product, TBAF (1.3 equiv, 20.5 mmol) was added to a THF solution of the silylated alkyne. After stirring 20 min at room temperature, the reaction mixture was diluted in ether, and washed with sat.NH_4Cl. Repeated extraction of the aqueous phase with ether, drying of the combined organic layers (Na_2SO_4), evaporation of the solvent and flash chromatography as described above afforded a second crop of the desired alkyne *(S)*-**2.040a**.

Alkyne *(S)*-**2.040a**: **$[\alpha]_D^{25}$** -95° (*c* 0.26, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ:7.30-7.15 (m, 5H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.24 (td, *J* = 5.5, 2.1 Hz, 1H), 3.79 (dd, *J* = 11.1, 5.5 Hz, 1H), 3.69 (dd, *J* = 11.1, 5.5 Hz, 1H), 2.7 (br, 1H), 2.43 (d, *J* = 2.1 Hz, 1H), 1.94 (dt, *J* = 11.1, 5.5 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ137.6, 128.7, 128.3, 128.2, 82.2, 74.9,

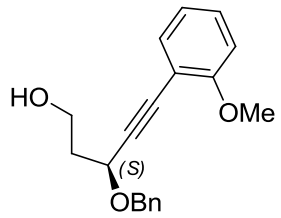
71.1, 67.6, 59.9 38.1; **IR ν_{max}** ($CHCl_3$, cast): 3590, 3566, 3545, 3483, 3439, 3417, 3404, 3396, 3391, 2343, 2088, 1646, 1634, 1251, 1053, 734, 697, 626, 603, 570 cm^{-1}; **HRMS** (ESI) Calculated $[M+H^+]$ $C_{12}H_{15}O_2$: 191.1072, Found: 191.1063.

Alkyne *(S)*-**2.040a': $[\alpha]_D^{25}$** -90° (c 0.3, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 400 MHz): δ:7.35-7.16 (m, 5H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.31 (d, *J* = 11.7 Hz, 1H), 4.15 (t, *J* = 6.0, 1H), 3.70 (dt, *J* = 11.2, 5.5 Hz, 1H), 3.58 (dt, *J* = 11.2, 5.5 Hz, 1H), 2.5 (br, 1H), 1.82 (dt, *J* = 11.2, 5.5 Hz, 2H), 0.1-0.0 (m, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz): 137.6, 128.6 (2C), 128.2, 127.9 (2C), 104.8, 103.6, 70.9, 68.2, 60.3, 38.0, 4.2 (3C); **IR ν_{max}** ($CHCl_3$, cast): 3590, 3566, 3545, 3483, 3439, 3417, 3404, 3396, 3391, 2343, 2088, 1646, 1634, 1251, 1053, 734, 697, 626, 603, 570 cm^{-1}; **HRMS** (ESI) Calculated $[M+H^+]$ $C_{15}H_{23}O_2Si$: 263.1467, Found: 263.1469.

Formation of tetrasubstituted helical alkene scope with varying aromatic substitutents

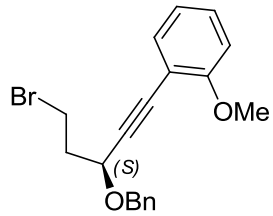


(S)-3-(benzyloxy)-5-(2-methoxyphenyl)pent-4-yn-1-ol (S)-**2.039a-intb**



The titled compound was prepared according to the general procedure for Sonogashira coupling. The crude compound was purified by a flash column (EtOAc: Hexane 1:3) to afford a tan oil in 83 % yield. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.40 (m, 3H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.29 (m, 2H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.4, 1H), 4.92 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.58 (t, *J* = 6.0 Hz, 1H), 3.89 (m, 2H), 3.86 (s, 3H), 2.79 (br, 1H), 2.12 (q, *J* = 11.2, 5.7 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.1, 137.7, 133.4, 129.9, 128.3, 128.1, 127.7, 120.3, 111.5, 110.5, 91.4, 83.2, 70.6, 68.1, 59.9, 55.6, 38.0; **IR ν_{max}** ($CHCl_3$, cast): 3417, 2956, 2873, 1596, 1489, 1454, 1292, 1026, 751, 699 cm^{-1}; **HRMS** (ESI) Calculated $[M+NH_4^+]$ $C_{19}H_{24}NO_3$: 314.17562, Found: 314.17616.

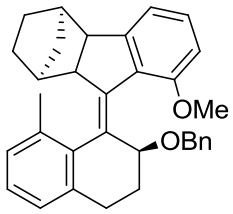
(S)-1-(3-(benzyloxy)-5-bromopent-1-ynyl)-2-methoxybenzene **2.049b**



The title compound was prepared according to the general procedure for Appel reaction. The crude compound was purified with a flash column chromatography on silica gel (Hexane/ EtOAc 10:1) to yield the desired product as a tan oil in 99% yield. **$[\alpha]_D^{25}$** -66° (*c* 0.25, DCM); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.4 Hz, 3H), 7.26 (t, J = 7.2 Hz, 2H), 7.21 (m, 2H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.82 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.48 (m, 1H), 3.78 (s, 3H), 3.54 (t, *J* = 6.8 Hz, 2H), 2.34 (m, 1H), 2.27 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.2, 137.8, 133.4, 129.9, 128.3, 128.1, 127.7, 120.3, 111.6, 110.6, 90.8, 83.2, 70.7, 67.5, 55.7, 38.7, 29.1; **IR** (CHCl3, cast): 3029, 2963, 2861, 1596, 1493, 1454, 1261, 1093,

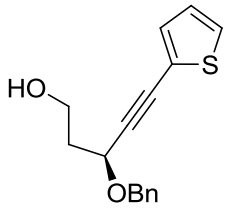
1025, 798, 752, 697 cm^{-1}; **HRMS** (ESI) Calculated $C_{19}H_{23}BrNO_2$ [M+NH_4^+]: 376.09122, Found: 376.09126.

Tetra-substituted alkene **2.050b**



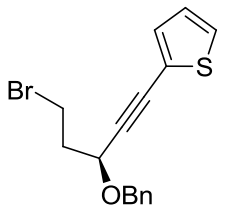
The title compound was prepared according to the general procedure for tetra-substituted alkene synthesis in 0.2 mmol scale. The crude compound was purified with a flash column chromatography on silica gel (Hexane/ EtOAc 10:1) to yield the desired product as a light tan gummy oil (70mg, 76%). d.r = 5.3:1; $\mathbf{[\alpha]_D^{28}}$ +126.8^o (c 1.20, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (m, 1H), 7.14 (t, *J* = 7.2 Hz, 4H), 7.06 (m, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 3H), 6.75 (d, J = 8.1 Hz, 1H), 5.84 (dd, *J* = 5.2, 2.6 Hz, 1H), 4.47 (q, *J* = 22.4, 12.2 Hz, 2H), 3.77 (s, 3H), 2.95 (q, *J* = 14.6, 7.9 Hz, 2H), 2.81 (m, 1H), 2.62 (q, *J* = 16.1, 8.1 Hz, 1H), 2.39 (s, 3H), 2.29 (m, 1H), 2.04 (m, 2H), 1.59 (d, *J* = 4.1 Hz, 1H), 1.46 (m, 1H), 1.26 (m, 1H), 1.19 (m, 1H), 1.04 (d, *J* = 9.9 Hz, 1H), 0.79 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.4, 153.3, 142.9, 140.1, 140.1, 138.9, 134.1, 133.9, 130.3, 129.6, 128.2, 128.0, 127.9, 127.0, 126.7, 126.6, 126.4, 124.5, 117.8, 109.1, 75.5, 68.9, 54.6, 53.5, 52.0, 43.6, 40.9, 32.5, 30.6, 29.2, 28.3, 26.4, 19.5; **IR $\mathbf{v_{max}}$** ($CHCl_3$, cast): 3027, 2946, 1576, 1496, 1464, 1448, 1264, 1176, 1095, 1071, 909, 732, 697, 648 cm^{-1}; **HRMS** (ESI) Calculated [M+Na^+] $C_{33}H_{34}NaO_2$: 485.2451, Found: 485.2443.

(S)-3-(benzyloxy)-5-(thiophen-2-yl)pent-4-yn-1-ol (S)-**2.039a-intc**



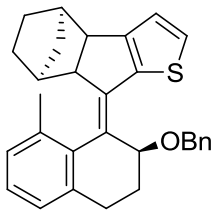
The titled compound was prepared according to the general procedure for Sonogashira coupling. The crude compound was purified by a flash column (EtOAc: Hexane 1:3) to afford a tan oil in 84 % yield, $\mathbf{[\alpha]_D^{25}}$ + 90° (*c* 0.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.27 (m, 1H), 7.22 (m, 2H), 6.94 (t, *J* = 4.0 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.54 (m, 2H), 3.88 (m, 1H), 3.77 (m, 1H) 2.56 (s, 1H), 2.07 (m, 2H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.4, 132.3, 128.3, 127.9, 127.8, 127.3, 126.8, 122.2, 91.2, 79.7, 70.8, 67.9, 59.7, 37.9; **IR ν_{max}** ($CHCl_3$, cast): 3420, 2929, 2869, 1639, 1498, 1456, 1332, 1189, 1064, 850, 734, 695 cm^{-1} ; **HRMS** (ESI) Calculated [$M+Na^+$] $C_{16}H_{16}NaO_2S$: 295.0763, Found: 295.0772.

(S)-2-(3-(benzyloxy)-5-bromopent-1-ynyl)thiophene **2.049c**



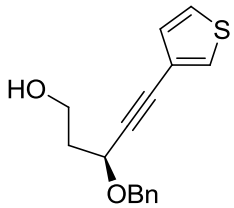
The title compound was prepared according to the general procedure for Appel reaction. The crude compound was purified with a flash column chromatography on silica gel (Hexane/ EtOAc 10:1) to yield the desired product as a light brown oil in 99% yield. $\mathbf{[\alpha]_D^{27}}$ -82.2^o (c 1.15 in $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.27 (m, 1H), 7.22 (m, 2H), 7.15 (m, 1H), 6.94 (t, *J* = 4.1 Hz, 1H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.54 (m, 1H), 4.52 (t, *J* = 2.5 Hz, 1H), 3.54 (m, 2H), 2.38 (m, 1H), 2.30 (m, 1H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.5, 132.4, 128.3, 128.0, 127.8, 127.4, 126.9, 122.1, 90.8, 79.8, 71.0, 67.4, 38.5, 29.0; **IR ν_{max}** ($CHCl_3$, cast): 3105, 3071, 3029, 2911, 2862, 2218, 1496, 1454, 1330, 1258, 1190, 1095, 1071, 1028, 851, 736, 697, 667 cm^{-1}; **HRMS** (ESI) Calculated [$M+NH_4^+$] $C_{16}H_{19}BrNOS$: 352.03707, Found: 352.03791.

Tetra-substituted alkene **2.050c**



The title compound was prepared according to the general procedure for for tetrasubstituted alkene synthesis in 0.2 mmol scale. The crude compound was purified with a flash column chromatography on silica gel (Hexane/ EtOAc 10:1) to yield the desired product as a tan gummy oil (80mg, 91%). d.r.= 6.7:1, $\mathbf{[\alpha]_D^{29}}$ +1.3^o (*c* 1.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.0 Hz, 1H), 7.22 (m, 3H), 7.17 (m, 2H), 7.11 (m, 2H), 7.00 (t, *J* = 3.7 Hz, 1H), 6.84 (d, *J* = 5.0 Hz, 1H), 5.22 (dd, *J* = 8.1, 3.2 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 3.27 (d, *J* = 6.5 Hz, 1H), 2.97 (d, *J* = 6.6 Hz, 1H), 2.60 (ddd, *J* = 14.2, 5.7, 1.6 Hz, 1H), 2.50 (m, 1H), 2.43 (s, 3H), 2.32 (m, 1H), 2.18 (m, 1H), 1.69 (m, 1H), 1.47 (m, 1H), 1.37 (m, 1H), 1.22 (m, 2H), 1.06 (d, *J* = 9.9 Hz, 1H), 0.87 (m, 1H), 0.79 (d, *J* = 9.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.5, 142.9, 141.7, 140.7, 139.1, 138.9, 136.8, 134.1, 130.4, 129.7, 128.4, 128.1, 127.5, 127.1, 126.4, 125.7, 123.7, 122.2, 77.4, 69.4, 57.8, 48.8, 41.5, 40.1, 32.2, 30.9, 28.7, 28.5, 28.0, 19.9; **IR $\mathbf{v_{max}}$** ($CHCl_3$, cast): 3029, 2948, 2869, 1471, 134, 1296, 1181, 1067, 909, 732 cm^{-1}; **HRMS** (ESI) Calculated [M+Na$^+$] $C_{30}H_{30}NaOS$: 461.1909, Found: 461.1920.

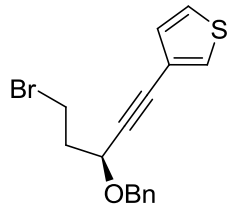
(S)-3-(benzyloxy)-5-(thiophen-3-yl)pent-4-yn-1-ol (S)-**2.039a-intd**



The title compound was prepared according to the general procedure for Appel reaction. The crude compound was purified with a flash column chromatography on silica gel (Hexane/ EtOAc 10:1) to yield the desired product as a tan oil in 94% yield. $\mathbf{[\alpha]_D^{27}}$ -82.2^o (*c* 1.15, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.9 Hz, 1H), 7.34 (m, 4H), 7.26 (m 1H), 7.21 (dd, *J* =

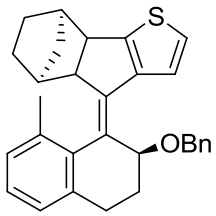
4.9, 3.0 Hz, 1H), 7.10 (d, *J* = 4.9 Hz, 1H), 4.84 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.51 (t, *J* = 6.2 Hz, 1H), 3.88 (m, 1H), 3.77 (m, 1H), 2.68 (br, 1H), 2.06 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.5, 129.8, 129.0, 128.3, 127.9, 127.7, 125.3, 121.3, 86.8, 81.6, 70.7, 67.8, 59.7, 38.0; **IR ν_{max}** ($CHCl_3$, cast): 3406, 3106, 2955, 2881, 1495, 1458, 1364, 1334, 1205, 1055, 783, 736, 697 cm^{-1}; **HRMS** (ESI) Calculated $[M+Na^+]$ $C_{16}H_{16}NaO_2S$: 295.0763, Found: 295.0763.

(S)-3-(3-(benzyloxy)-5-bromopent-1-ynyl)thiophene **2.049d**



The title compound was prepared according to the general procedure for Appel reaction. The crude compound was purified with a flash column chromatography on silica gel (Hexane/ EtOAc 10:1) to yield the desired product as a light brown oil in 99% yield. **$[\alpha]_D^{27}$** -77.8^o (*c* 1.15, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 2.9 Hz, 1H), 7.35 (m, 4H), 7.27 (m, 1H), 7.22 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.10 (d, *J* = 4.9 Hz, 1H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.50 (dd, *J* = 7.4, 5.5 Hz, 1H), 3.56 (q, *J* = 13.4, 6.9 Hz, 2H), 2.38 (m, 1H), 2.30 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.6, 129.8, 129.2, 128.3, 127.9, 127.7, 125.4, 121.3, 86.4, 81.7, 70.9, 67.3, 38.6, 29.1; **IR ν_{max}** (CHCl3, cast): 3106, 3029, 2861, 2224, 1496, 1454, 1358, 1332, 1258, 1207, 1181, 1152, 1095, 1063, 783, 735, 697, 667, 624cm^{-1}; **HRMS** (ESI) Calculated $[M+NH_4^+]$ $C_{16}H_{19}BrNOS$: 352.03707, Found: 352.03675.

Tetra-substituted alkene **2.050d**



The title compound was prepared according to the general procedure for for tetrasubstituted alkene synthesis in 0.2 mmol scale. The crude compound was purified with a flash column chromatography on silica gel (Hexane/ EtOAc 10:1) to yield the desired product as a tan gummy oil (64mg, 73%). d.r.= 5:1, $\mathbf{[\alpha]_D^{29}}$ +6.9^o (*c*1.50, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.24 (m, 3H), 7.19 (m, 3H), 7.12 (d, *J* = 4.5 Hz, 2H), 7.06 (d, *J* = 5.2 Hz, 1H), 7.00 (t, *J* = 4.2 Hz, 1H), 5.34 (dd, *J* = 8.3, 3.9 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 3.30 (d, *J* = 6.6 Hz, 1H), 3.09 (d, *J* = 6.6 Hz, 1H), 2.60 (ddd, *J* = 14.1, 5.6, 2.0 Hz, 1H), 2.44 (s, 3H), 2.31 (m, 2H), 2.20 (d, J = 3.7 Hz, 1H), 1.66 (tt, *J* = 12.3, 4.8 Hz, 1H), 1.46 (tt, *J* = 11.9, 4.3 Hz, 1H), 1.35 (m, 1H), 1.26 (m, 2H), 1.17 (m, 1H), 1.10 (d, *J* = 10.0 Hz, 1H), 0.80 (d, *J* = 10.1 Hz, 1H) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.2, 146.5, 142.1, 140.9, 139.2, 138.9, 137.2, 134.1, 128.6, 128.4, 128.2, 128.1, 127.4, 127.1, 126.4, 125.4, 123.6, 122.2, 75.3, 68.5, 58.9, 49.0, 42.8, 40.1, 32.3, 30.8, 28.5, 28.3, 28.1, 19.8; **IR $\mathbf{v_{max}}$** ($CHCl_3$, cast): 2948, 2869, 1495, 1454, 1328, 1264, 1175, 1089, 734, 652 cm^{-1}; **HRMS** (ESI) Calculated [M+Na$^+$] $C_{30}H_{30}NaOS$: 461.1909, Found: 461.1906.

Section 2.2

General procedure for Sonogashira coupling:

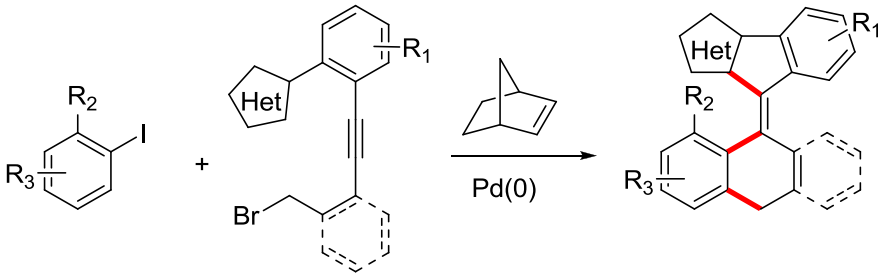
Method A: To the corresponding aryl iodides (1.0 equiv) in Et_3N (5 mL/mmol) were added subsequently $PdCl_2(PPh_3)_2$ (5 mol %), CuI (1.2–5 mol %) and 4-pentyn-1-ol (1.2 equiv) at 25 °C under argon. Stirring was continued for 16 h at 25 °C. The reaction mixture was treated with satd. NH_4Cl solution and the resulting mixture was extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and concentration of the appropriate fractions *in vacuo* afforded the desired compounds.

Method B: To the corresponding aryl bromides (1.0 equiv) in Et_3N (5 mL/mmol) were added subsequently $PdCl_2(PPh_3)_2$ (5 mol %), CuI (1.2 mol %) and 4-pentyn-1-ol (1.5 equiv) at 25 °C under argon. The reaction was refluxed at 90 °C under argon for 16-24 h. The reaction mixture was treated with satd. NH_4Cl solution and the resulting mixture was extracted with DCM. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and concentration of the appropriate fractions *in vacuo* afforded the desired compounds.

General procedure for the synthesis of alkyl bromides via Appel reaction:

To the corresponding alcohols (1.0 equiv) and CBr_4 (1.2 equiv) in CH_2Cl_2 (3–5 mL/mmol) was added PPh_3 (1.2 equiv) in small portions. The reaction mixture was left to stir for 1 h at room temperature. Thereafter, the solvent was removed *in-vacuo*, the crude product was purified by silica gel flash chromatography, and concentration of the appropriate fractions *in-vacuo* afforded the desired compounds.

Synthesis of tetrasubstituted helical alkenes not bearing norbornene



General Procedure:

Ortho-substituted aryl iodide (2.0 equiv), the appropriate bromoalkyl aryl alkyne (1.0 equiv), palladium acetate (10 mol%), triphenylphosphine (20 mol%), cesium carbonate (3.0 equiv), and norbornene (2.0 equiv) were submitted to a sealable microwave tube. After adding freshly distilled acetonitrile (1 mL solvent / 0.1 mmol substrate), the reaction mixture was purged with argon for approx. 5 min. Afterwards, the microwave tube was sealed and immersed in a pre-heated oil bath (90 °C) for 24 h. Thereafter, the reaction mixture was cooled to room temperature, diluted with dichloromethane and then filtered through a short pad of Celite. After removing the solvent under reduced pressure the crude material was purified by flash chromatography.

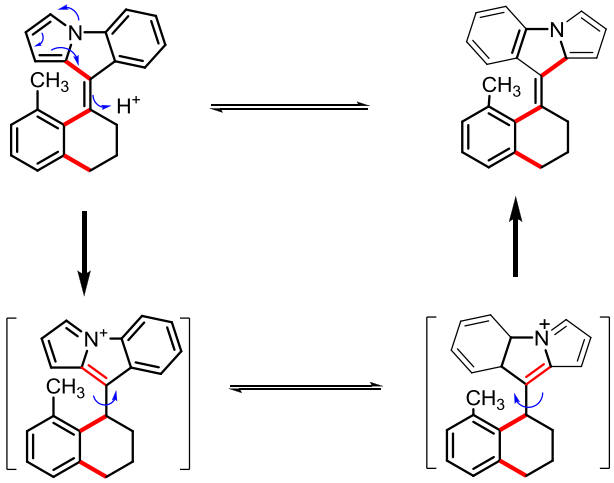
Note:

*1) Compounds **2.059a-g, 2.061a-e,i, and 2.065-2.067** were purified using Et_3N neutralized silica gel because they can be isomerized under acidic conditions.*

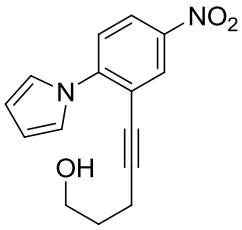
2) For all the tetra-substituted alkenes, the reaction and purification were carried out with protection from light, because the products are sensitive to light over time.

3) All tetra-substituted alkenes were characterized in CD_2Cl_2 for NMR and not $CDCl_3$.

The double bond in the tetra-substituted alkenes can be isomerized under acidic conditions. The mechanism for the isomerization is proposed as following:

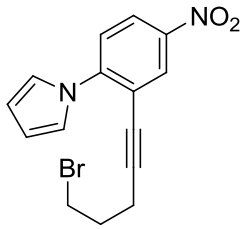


5-(4-nitro-2-(1H-pyrrol-1-yl)phenyl)pent-4-yn-1-ol **2.060c'**



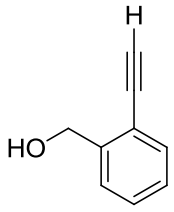
The title compound was prepared according to the general procedure for Sonogashira reaction (Method B) using the corresponding aryl bromide (1.00g, 3.74 mmol). Flash chromatography purification (Hexane/EtOAc 3:1) yielded the product as a tan oil (0.60 g, 59%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.15 (d, J = 2.3 Hz, 1H), 8.08 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.12 (t, *J* = 2.1 Hz, 2H), 6.36 (t, *J* = 2.2 Hz, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 1.80 (quint., *J* = 6.1 Hz, 2H), 1.39 (br s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 147.0, 142.5, 134.5, 125.1, 121.5, 120.8, 119.9, 110.2, 100.3, 77.0, 61.2, 30.5, 16.2; **IR ν_{max}** 3362, 2948, 2225, 1520, 1496, 1346, 1065, 863, 728; **HRMS** (ESI): Calculated $[M+H^+]$ $C_{15}H_{15}N_2O_3$: 271.1077, Found: 271.1086.

1-(2-(5-bromopent-1-ynyl)-5-nitrophenyl)-1H-pyrrole **2.060c**



The title compound was prepared according to the general procedure for the Appel reaction using the corresponding alcohol (600 mg, 2.22 mmol). Flash chromatography purification (Hexane/EtOAc 4:1) yielded the product as a dark tan oil (703 mg, 95%). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.16 (m, 1H), 8.08 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.11 (t, *J* = 2.1 Hz, 2H), 6.37 (t, *J* = 2.1 Hz, 2H), 3.43 (t, *J* = 6.4 Hz, 2H), 2.62 (t, *J* = 6.7 Hz, 2H), 2.08 (quint., *J* = 6.6 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 147.1, 142.6, 134.6, 124.8, 121.4, 120.7, 119.9, 110.4, 98.7, 77.6, 32.1, 30.7, 18.4; **IR ν_{max}** 3105, 2943, 2228, 1516, 1346, 1120, 1065, 862; **HRMS** (ESI): Calculated $[M+H^+]$ $C_{15}H_{14}BrN_2O_2$: 333.0239, Found: 333.0238.

(2-ethynylphenyl)methanol **2.060i''**

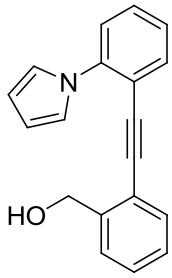


The title compound was prepared according to the standard Sonogashira condition (Method A) as prepared in the literature procedure[136]. Follwing this, the crude was subjected to TBAF deprotection (in 10 mL THF, 1.2 equiv. TBAF, 2h, r.t.), which was then quenched with water, extracted with EtOAc, washed with brine, dried with $MgSO_4$, and the organic evaporated under reduced pressure. The crude was subjected to flash chromatography (Hexanes:EtOAc 3:1) to

[136] Nugent, B.M.; Williams, A.L.; Prabhakaran, E.N. *Tetrahedron* **2003**, *59*, 8877.

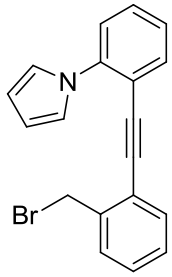
yield the compound as a dark yellow oil (900 mg, 67% yield over 2 steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.31 (dd, *J* = 8.4, 7.6 Hz, 1H), 7.21 (dd, *J* = 8.3, 7.6 Hz, 1H), 4.78 (s, 2H), 3.48 (br s, 1H), 3.33 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 143.0, 132.4, 128.9, 126.9, 126.7, 119.7, 81.9, 81.0, 62.9; Data correlates to literature.

(2-((2-(1H-pyrrol-1-yl)phenyl)ethynyl)phenyl)methanol **2.060i'**



The title compound was prepared according to the general procedure for the Sonogashira reaction (Method B). The crude compound was purified by flash chromatography on silica gel (Hexanes/EtOAc 3:1) to yield a tan oil (500 mg, 61 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.39 (m, 2H), 7.35 (m, 1H), 7.32 (m, 1H), 7.30 (m, 1H), 7.25 (m, 1H), 7.10 (t, *J* = 2.2 Hz, 2H), 6.37 (t, *J* = 2.1 Hz, 2H), 4.63 (s, 2H), 1.98 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.6, 142.0, 133.6, 132.4, 129.4, 128.9, 127.7, 127.4, 126.7, 125.5, 121.9, 121.2, 118.7, 109.4, 91.3, 90.6, 63; **IR ν_{max}** 3347, 3064, 2927, 1569, 1484, 1447, 1332, 1070, 1015, 757; **HRMS** (ESI): Calculated $[M+H^+]$ $C_{19}H_{16}NO$: 274.1232, found 274.1244.

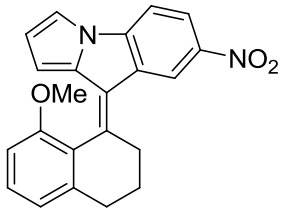
1-(2-((2-(bromomethyl)phenyl)ethynyl)phenyl)-1H-pyrrole **2.060i**



The title compound was prepared according to the general procedure for the Appel reaction. The crude residue was purified by flash chromatography on silica gel (Hexanes/EtOAc, 4:1) to yield the product as a dark brown solid (560 mg, 97%). **m.p.** 65-67 ^oC; **^{1}H NMR** (400 MHz, $CDCl_3$) δ

7.81 (ddd, *J* = 7.7, 1.5, 0.4 Hz, 1H), 7.55 (m, 1H), 7.48 (m, 2H), 7.44 (m, 1H), 7.41 (m, 1H), 7.37 (m, 1H), 7.33 (m, 1H), 7.30 (t, *J* = 2.2 Hz, 2H), 6.52 (t, *J* = 2.2 Hz, 2H), 4.66 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.6, 139.1, 133.7, 132.4, 129.6, 129.3, 128.8, 128.2, 126.3, 125.0, 122.5, 121.6, 118.0, 109.4, 91.7, 90.7, 32.0; **IR ν_{max}** 3063, 1568, 1486, 1446, 1332, 1223, 1070, 1015, 726; **HRMS** (ESI): Calculated [$M+H^+$] $C_{19}H_{15}BrN$: 336.0388, Found: 336.0390.

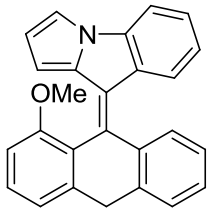
(Z)-9-(8-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)-7-nitro-9H-pyrrolo[1,2-a]indole **2.061c**



The title compound was prepared according to the general procedure for the synthesis of tetra-substituted alkenes (0.2 mmol scale)*. The crude residue was purified by flash chromatography on Et_3N neutralized silica gel (Hexane/DCM, 10:1) to yield the product (*E/Z* isomers with ratio of 1:1) as a orange solid (28 mg, 39%). **m.p.** 99-101 ^oC; **^{1}H NMR** (CD_2Cl_2, 400 MHz) (*E/Z* isomers): δ 8.05 (m, 2H), 8.02 (dd, *J* = 6.3, 2.2 Hz, 1H), 7.93 (m, 1H), 7.76 (dd, *J* = 6.5, 2.2 Hz, 1H), 7.35 (m, 1H), 7.31 (m, 1H), 7.25 (m, 2H), 7.08 (d, *J* = 2.7 Hz, 1H), 6.92 (m, 1H), 6.87 (m, 3H), 6.50 (t, *J* = 3.2 Hz, 1H), 6.39 (d, J = 3.5 Hz, 1H), 6.22 (t, *J* = 3.0 Hz, 1H), 5.69 (d, *J* = 3.5 Hz, 1H), 5.31 (m, 1H), 3.71 (s, 3H), 3.58 (s, 3H), 3.39 (m, 1H), 3.12 (m, 2H), 2.82 (m, 1H), 2.73 (m, 2H), 2.42 (dd, *J* = 9.6, 4.0 Hz, 1H), 2.37 (m, 1H), 2.32 (dd, *J* = 10.1, 3.8 Hz, 1H), 2.20 (m, 3H); **^{13}C NMR** (100 MHz, CD_2Cl_2) (E/Z isomers) δ 157.9, 156.9, 147.2, 147.1, 145.2, 144.7, 140.3, 139.4, 139.2, 138.6, 137.4, 137.1, 134.7, 134.5, 130.3, 130.1, 126.3, 125.3, 124.9, 124.5, 124.4, 124.3, 120.2, 119.8, 118.6, 118.5, 115.6, 115.4, 112.3, 111.1, 109.1, 107.6, 104.9, 104.8, 104.3, 55.5, 55.3, 32.4, 31.2, 31.0, 30.5, 22.5, 22.1; **IR ν_{max}** 2945, 1581, 1520, 1489, 14712, 1339, 1265, 1084, 735; **HRMS** (ESI) Calculated [$M+H^+$] $C_{22}H_{19}N_2O_3$: 359.1396, found 359.1405.

* *Using PPh_3 as a ligand instead of TFP, the reaction afforded the desired compound in 25% yield (E/Z isomer 1:1).*

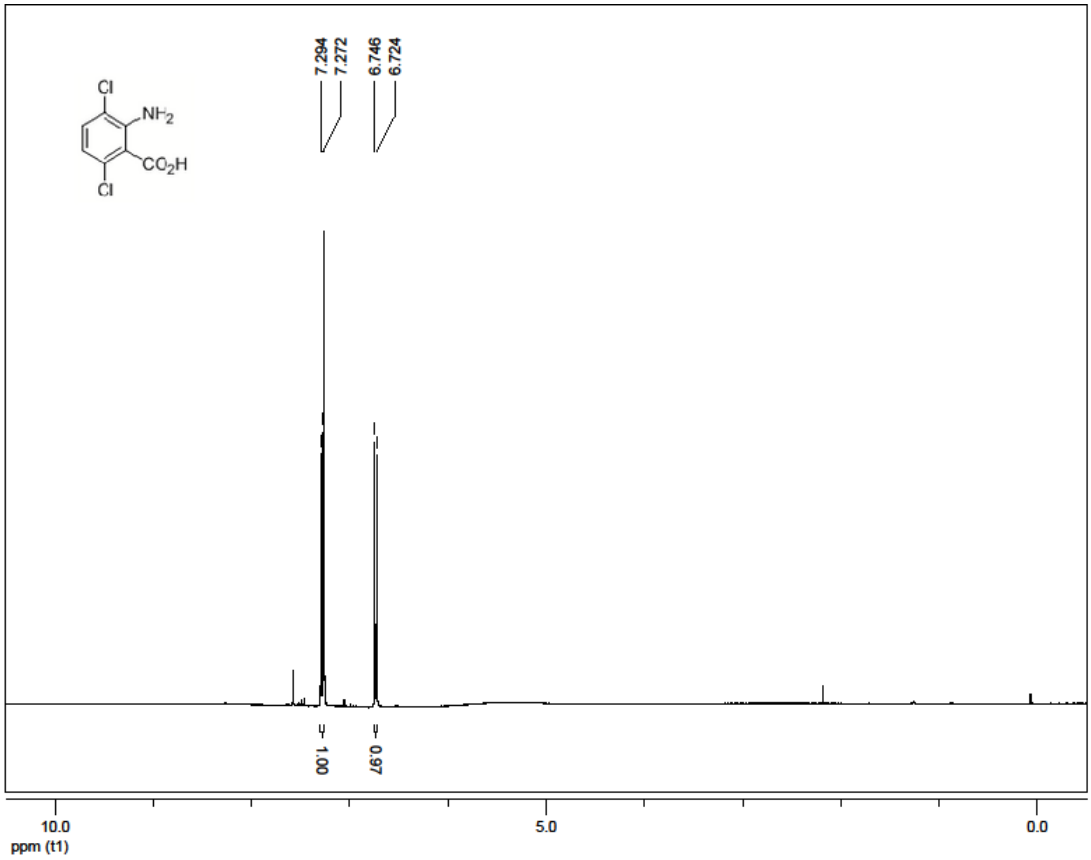
(Z)-9-(1-methoxyanthracen-9(10H)-ylidene)-9H-pyrrolo[1,2-a]indole **2.061i**



The title compound was prepared according to the general procedure for the synthesis of tetrasubstituted alkenes (0.2 mmole scale). The crude residue was purified by flash chromatography using silica gel (Hexane/DCM, 10:1) to yield the product as a velvet green solid (30 mg, 42%) (*E/Z* isomer 1:1). **m.p.** 95-97 ^{o}C; **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.03 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.83 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.77 (dt, *J* = 8.0, 0.8 Hz, 1H), 7.40 (m, 2H), 7.31 (m, 1H), 7.29 (m, 2H), 7.27 (m, 2H), 7.25 (m, 2H), 7.23 (s, 1H), 7.22 (d, *J* = 0.8 Hz, 1H), 7.21 (m, 1H), 7.07 (m, 2H), 7.04 (m, 1H), 7.02 (m, 1H), 7.00 (m, 1H), 6.89 (m, 1H), 6.87 (m, 1H), 6.85 (m, 1H), 6.49 (dd, *J* = 3.6, 1.0 Hz, 1H), 6.25 (dd, *J* = 3.6, 2.8 Hz, 1H), 6.20 (dd, *J* = 3.6, 2.7 Hz, 1H), 5.89 (dd, *J* = 3.6, 1.0 Hz, 1H), 5.31 (t, *J* = 1.1 Hz, 1H), 3.83 (m, 2H), 3.81 (s, 3H), 3.76 (s, 2H), 3.73 (s, 3H); **^{13}C NMR** (All Signals) (100 MHz, CD_2Cl_2) δ 156.4, 141.69, 138.8, 128.9, 128.7, 128.6, 128.6, 128.4, 127.5, 127.5, 127.4, 127.3, 125.7, 125.5, 125.4, 125.2, 123.2, 123.0, 120.0, 119.6, 114.4, 113.8, 112.3, 111.7, 109.8, 109.4, 109.1, 109.1, 107.1, 106.6, 55.6, 38.0, 32.0, 23.1, 14.3 **IR ν_{max}** 2951, 1618, 1489, 1261, 1084, 953, 770, 710; **HRMS** (ESI) Calculated $[M+H^+]$ $C_{26}H_{20}NO$: 362.1545, Found: 362.1551.

Spectral Data

Chapter 1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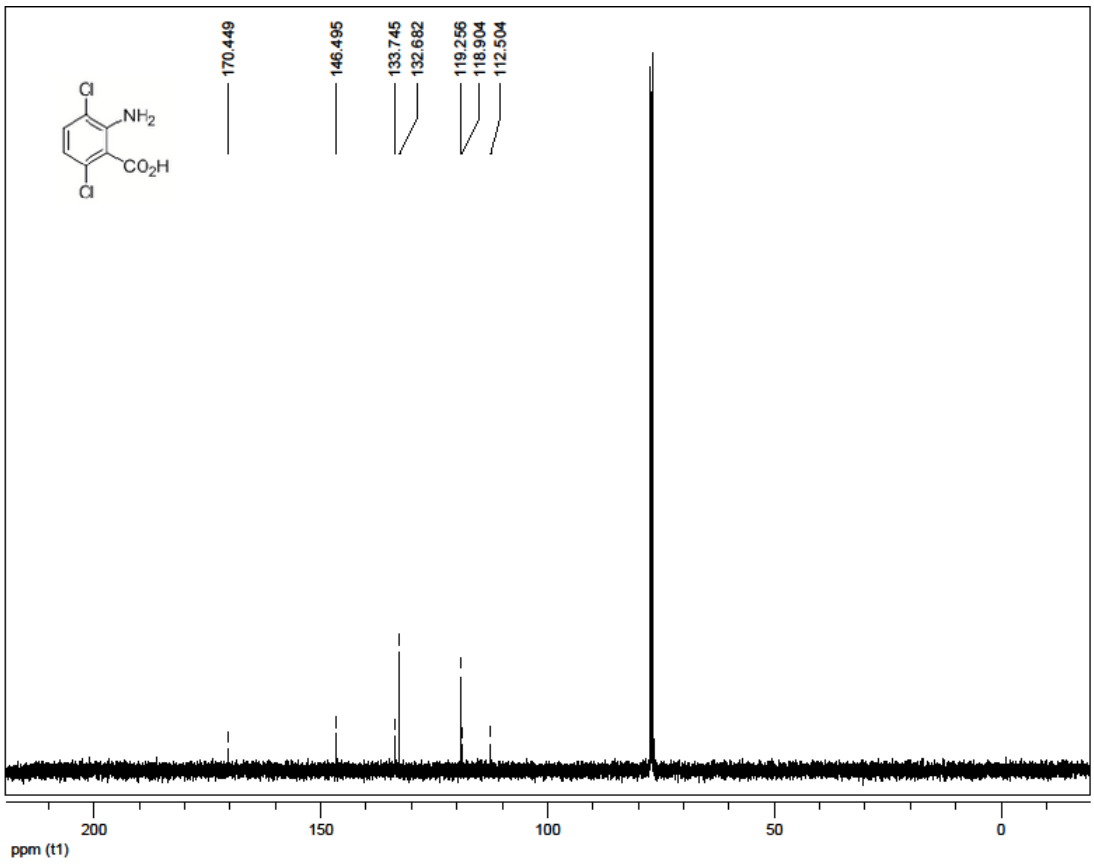
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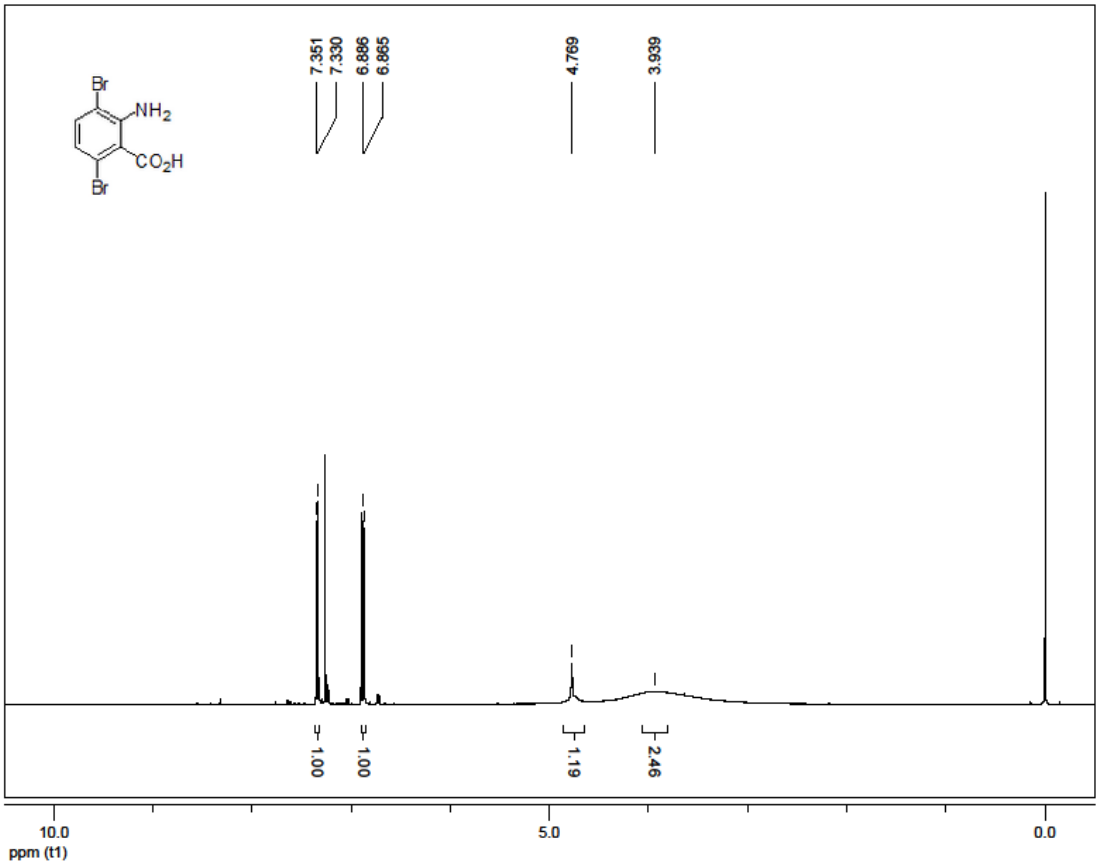
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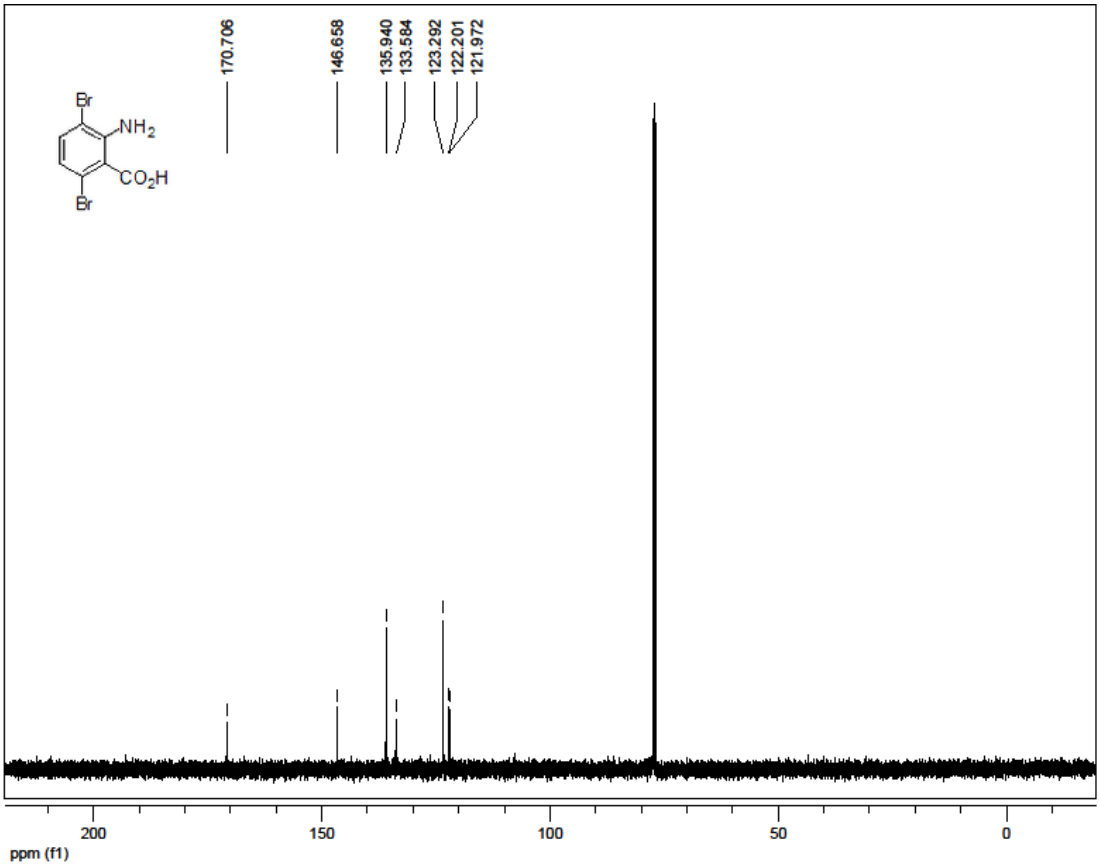
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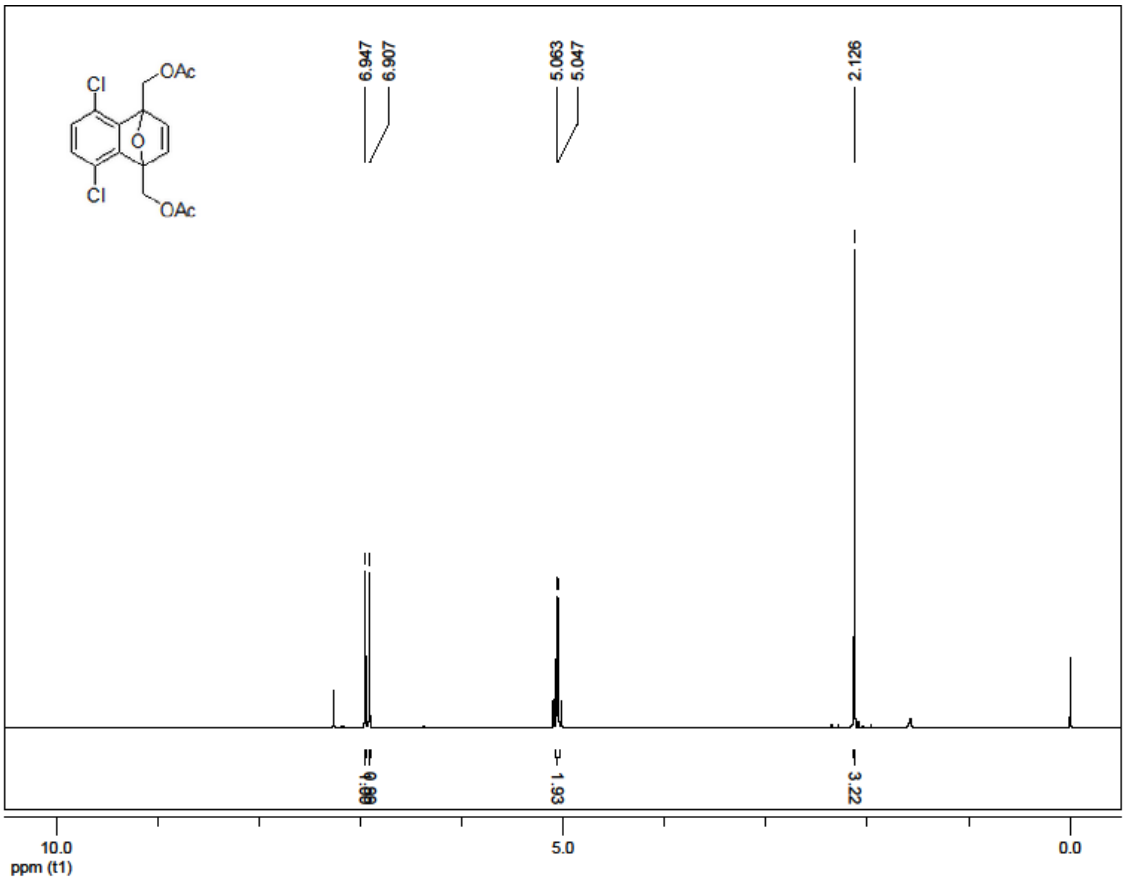
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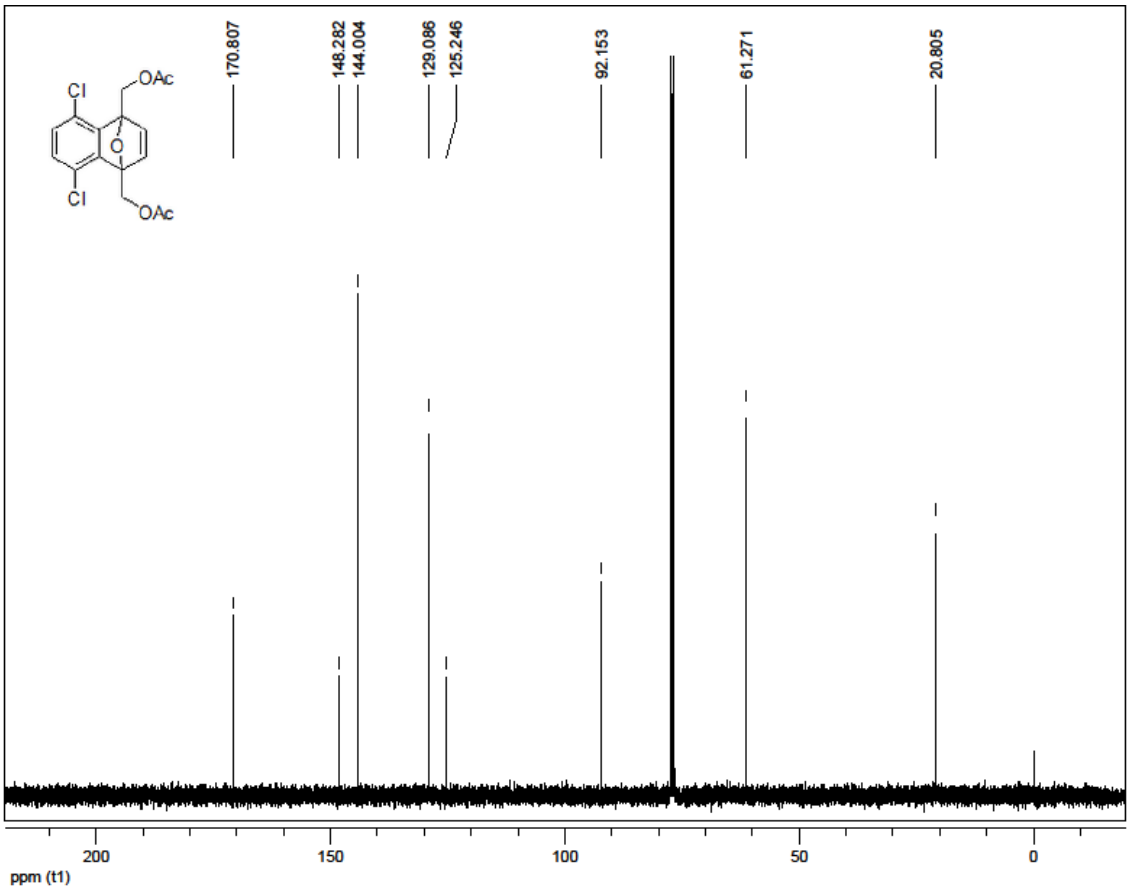
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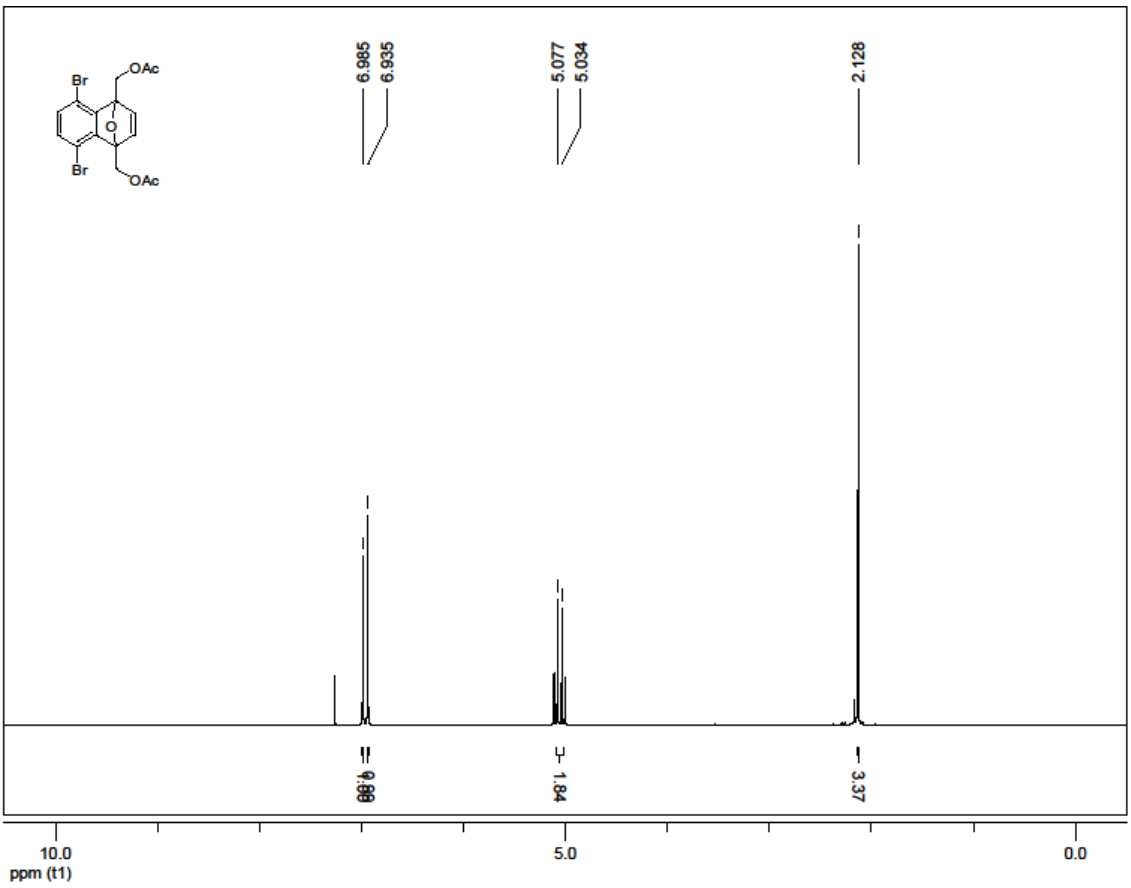
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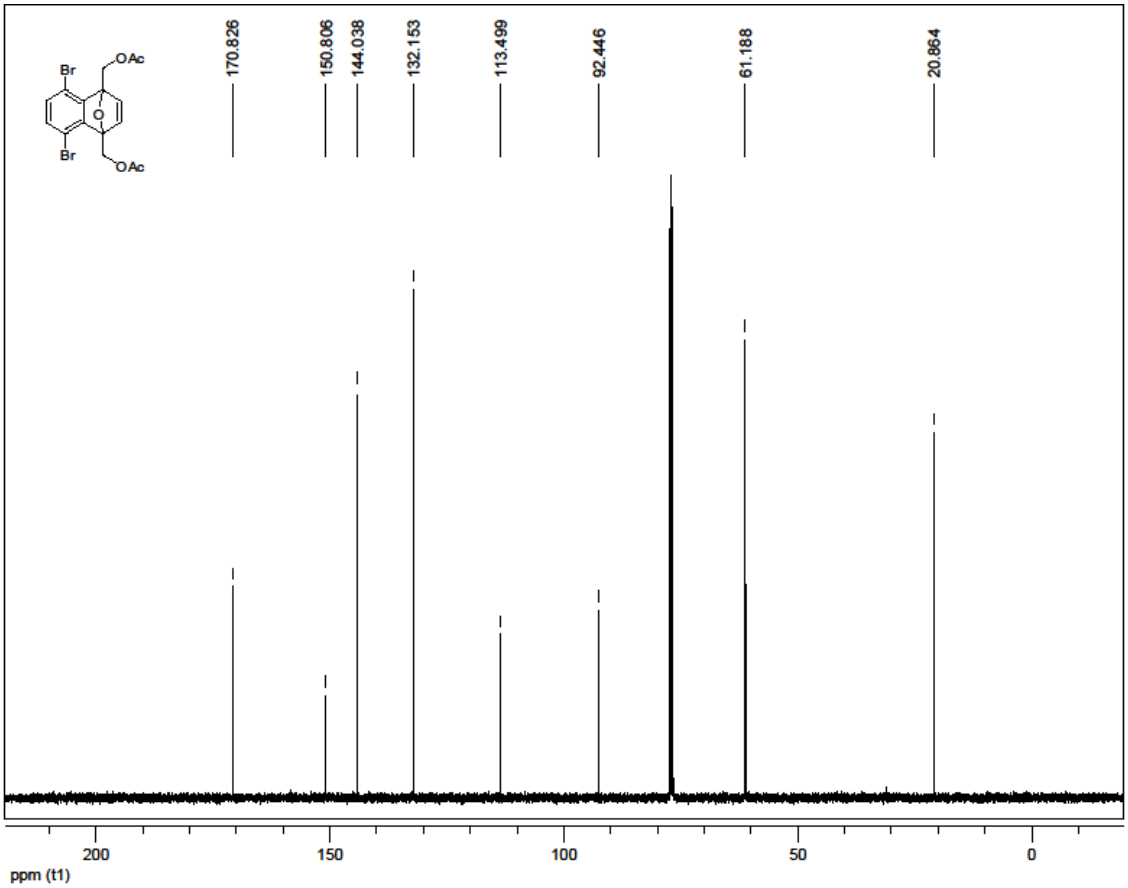
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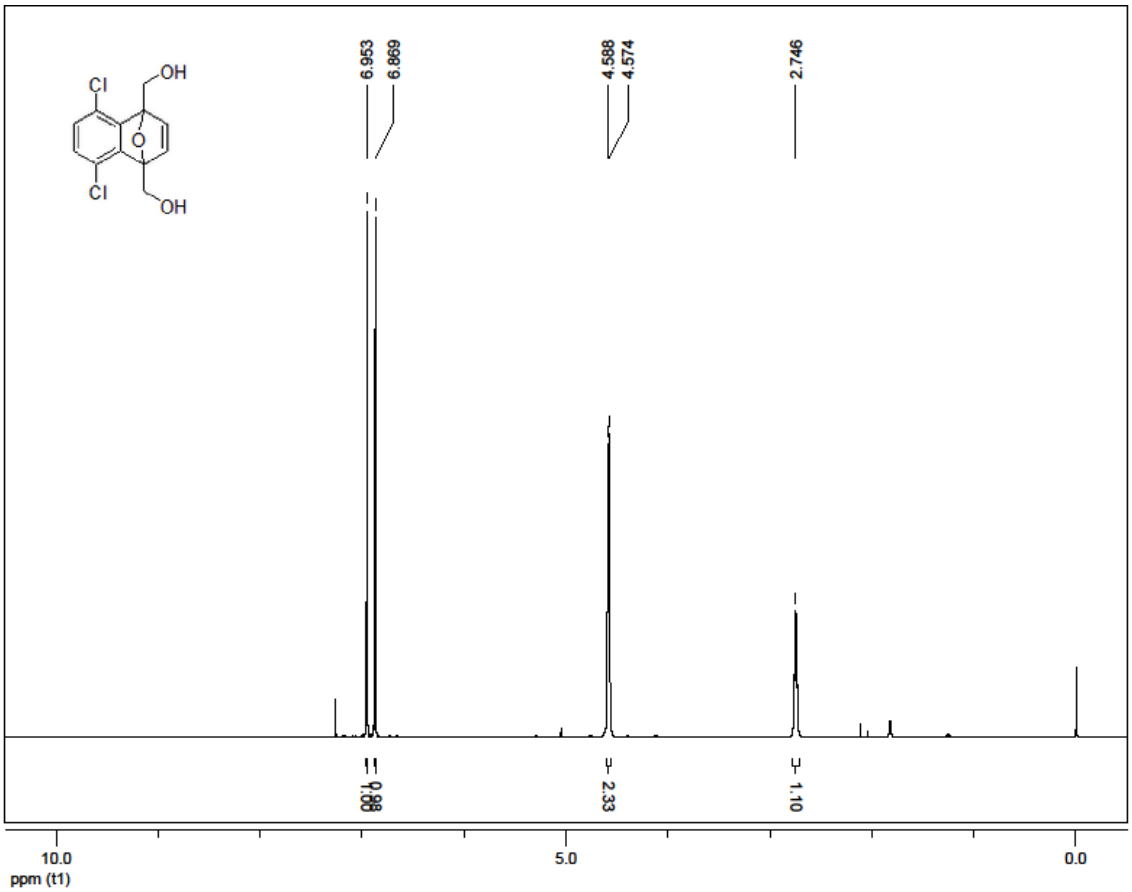
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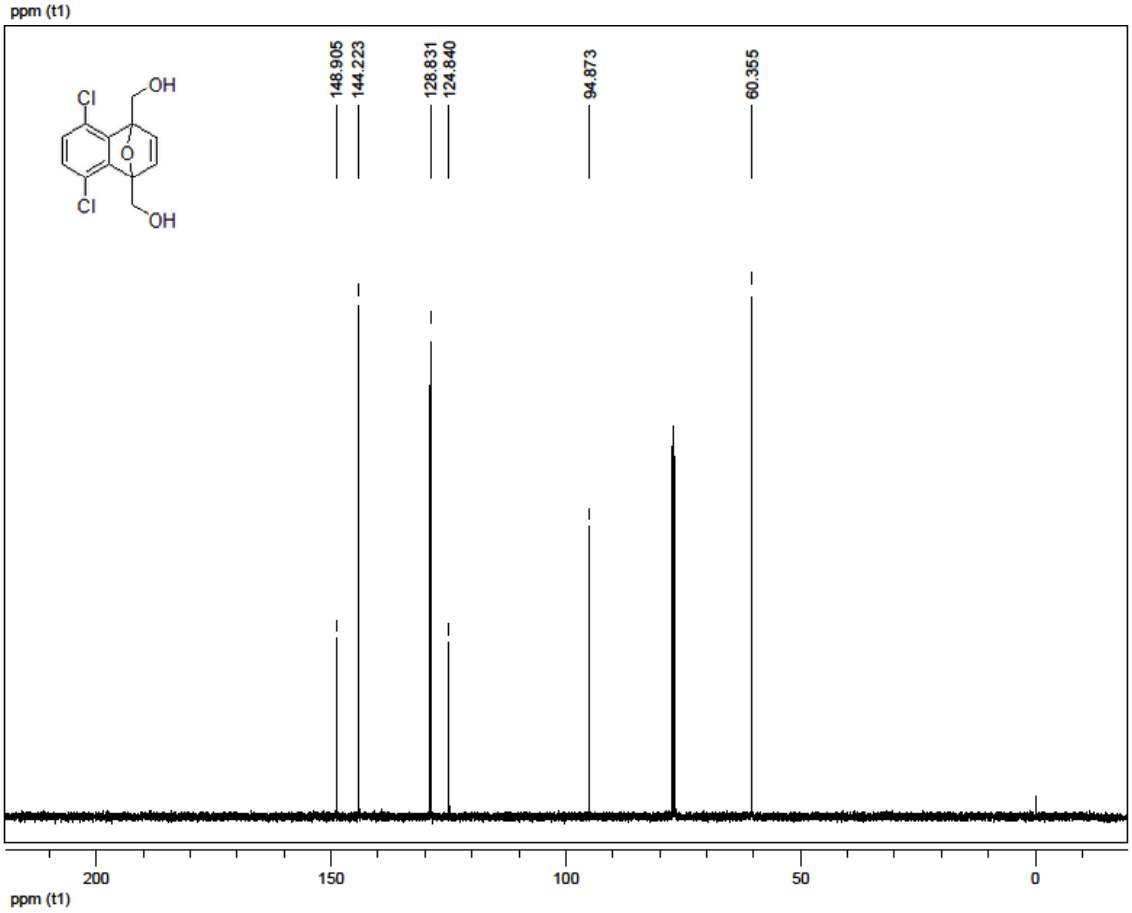
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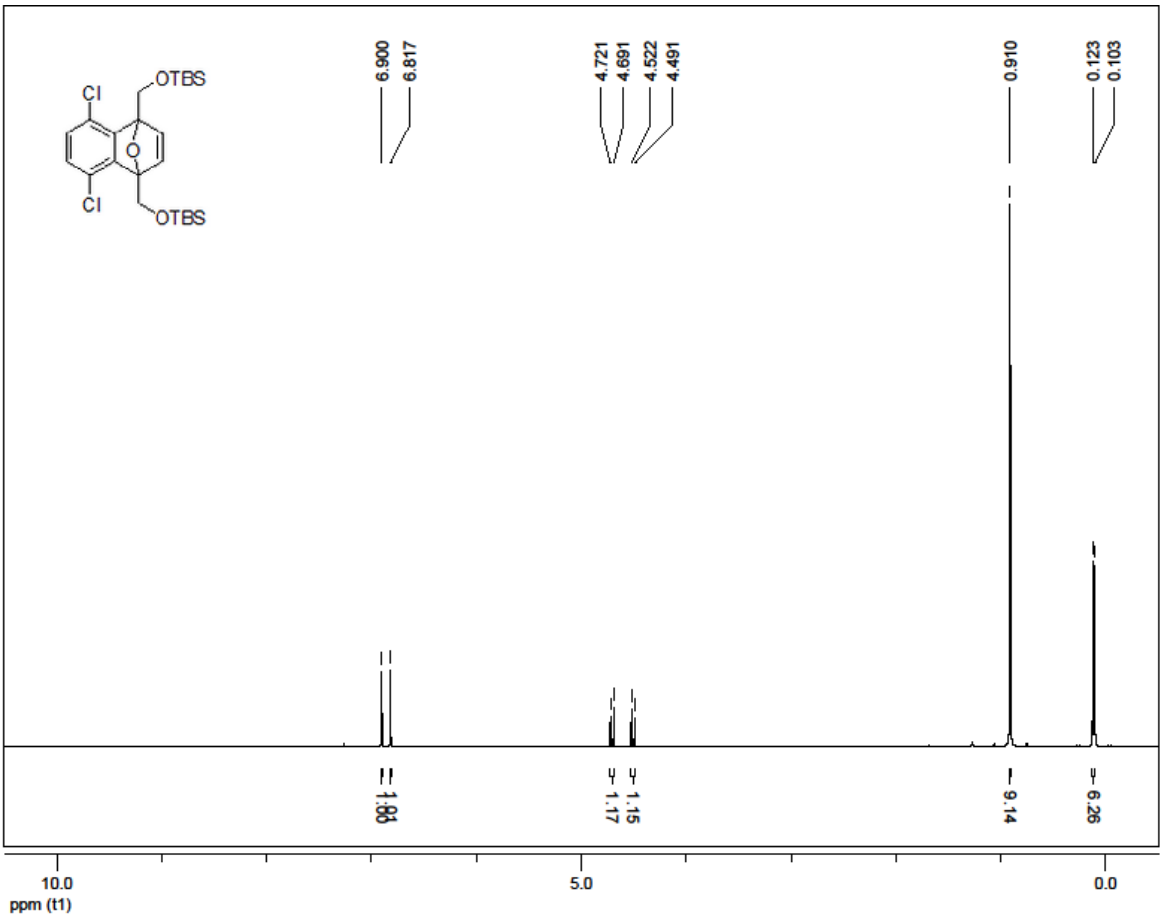
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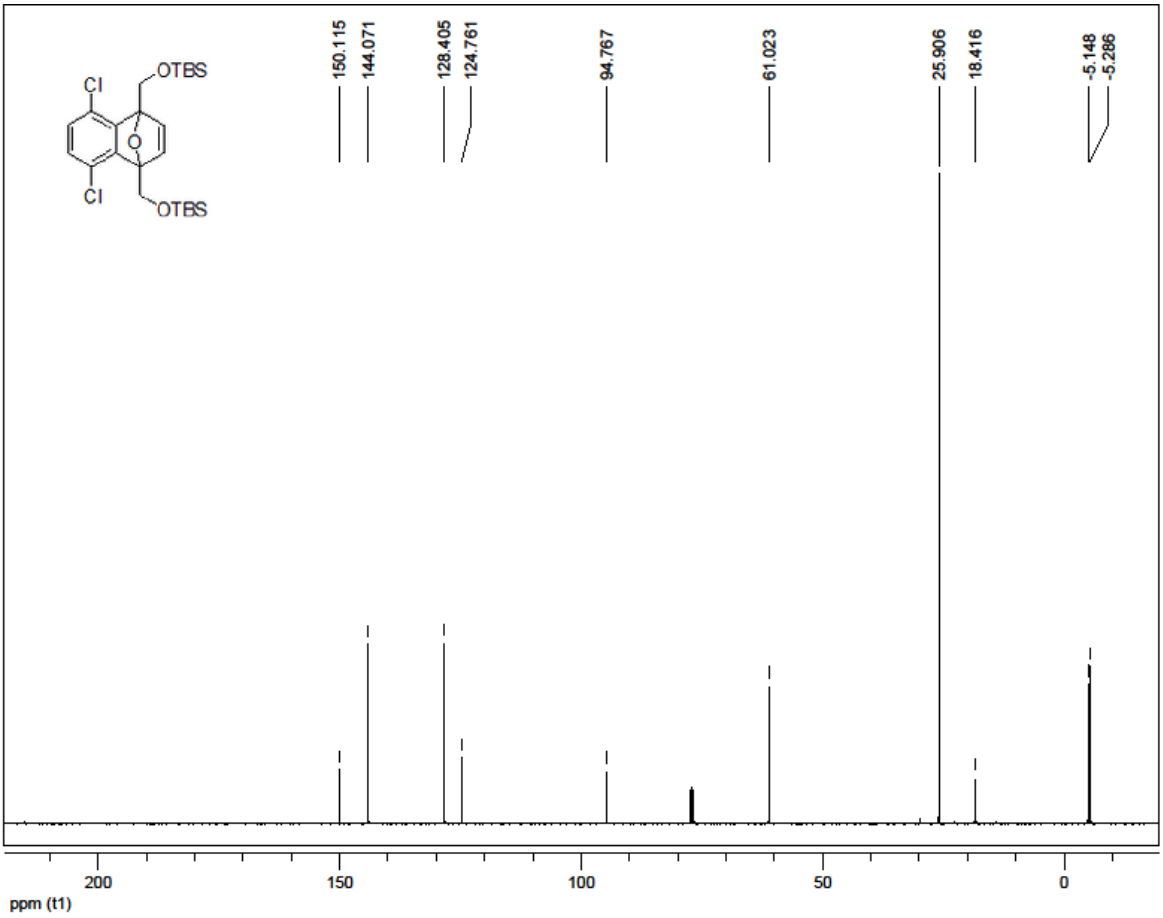
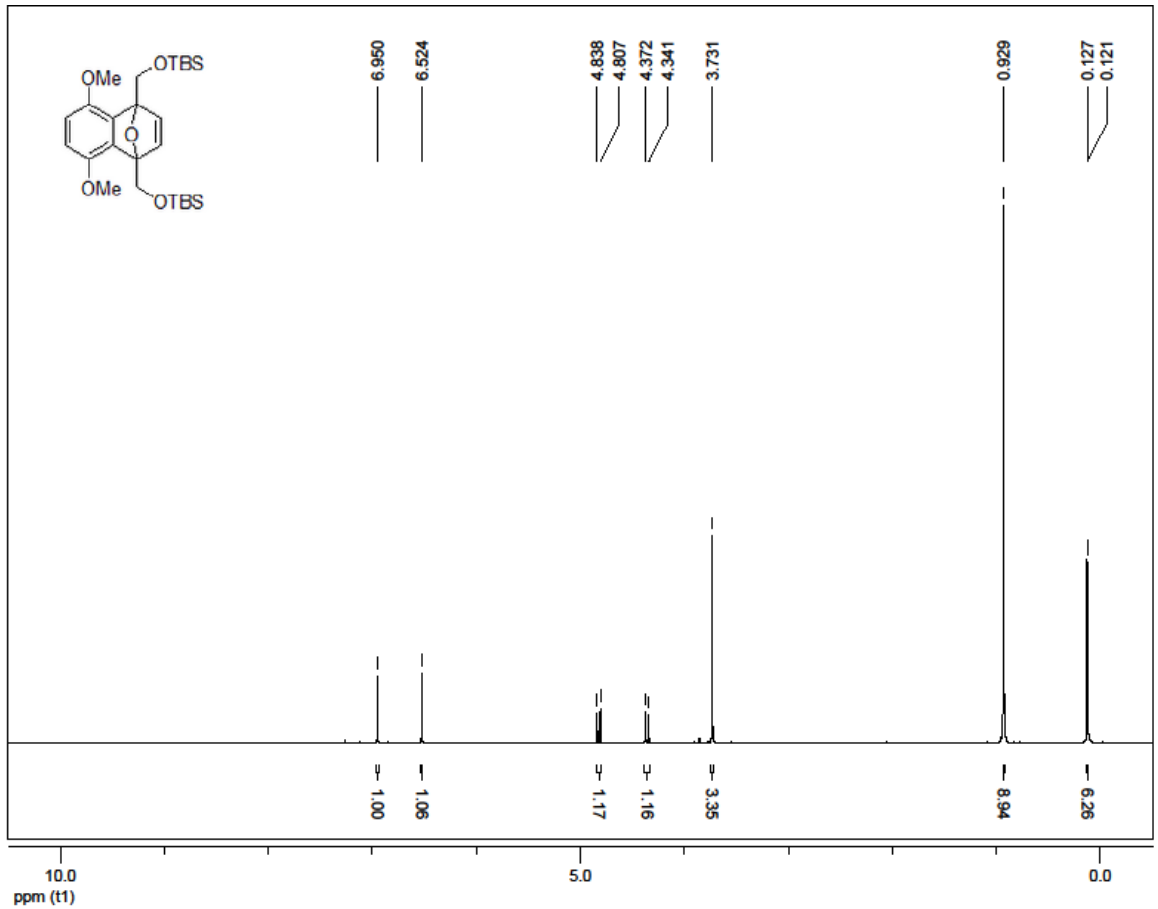
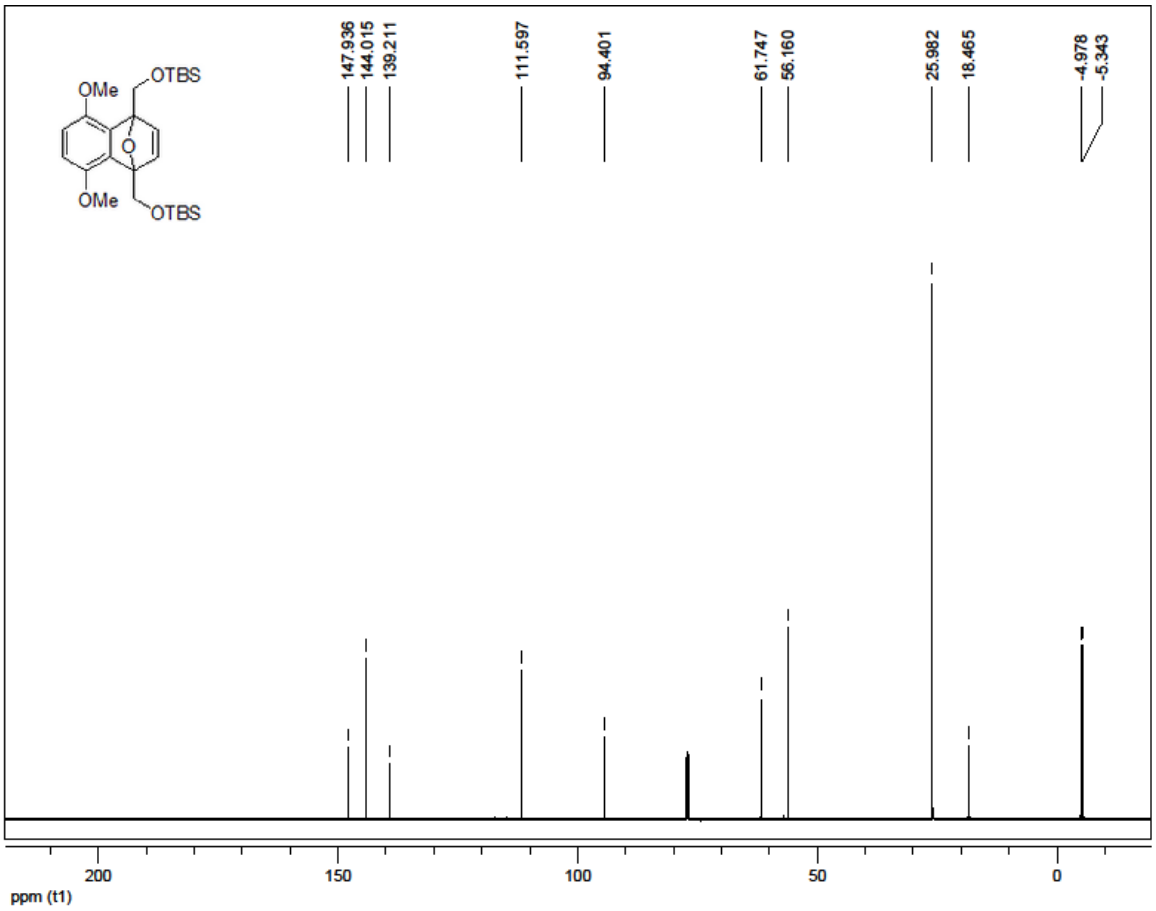
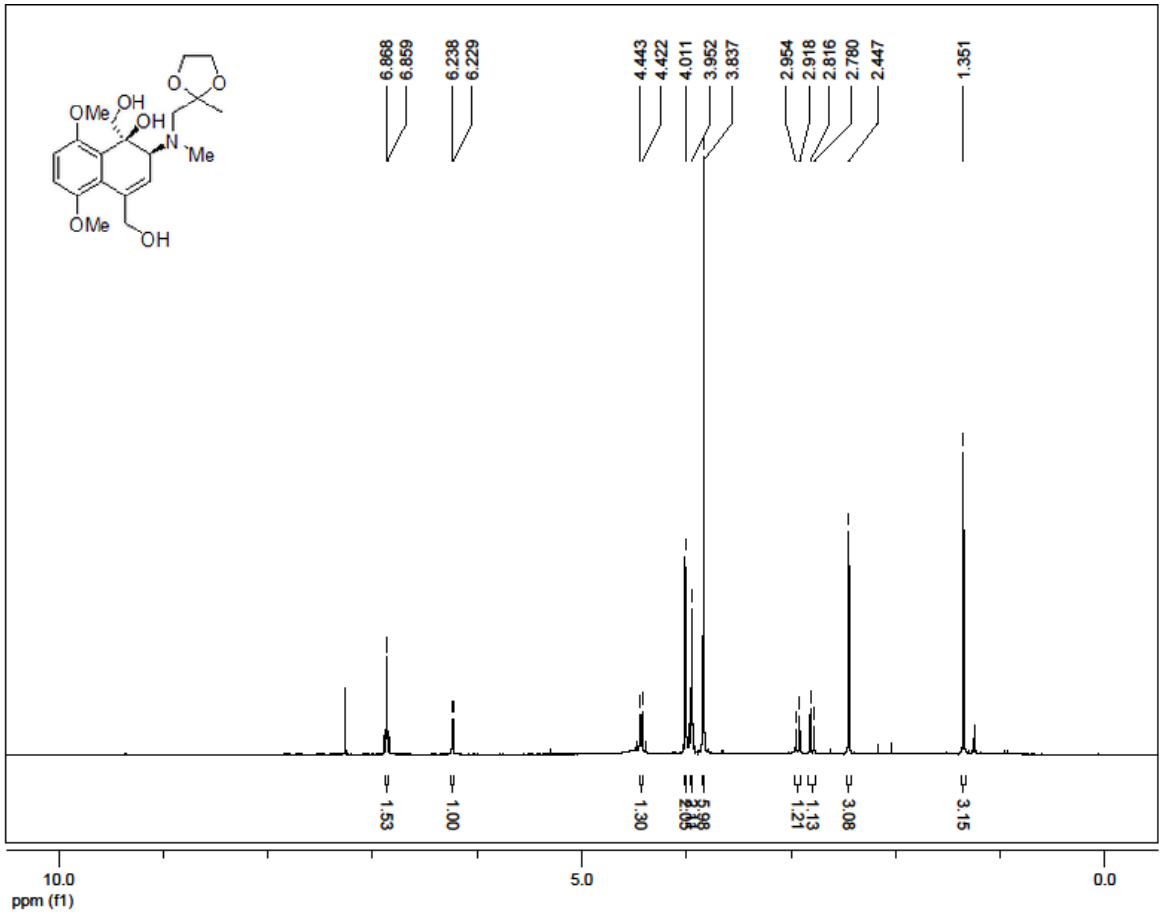
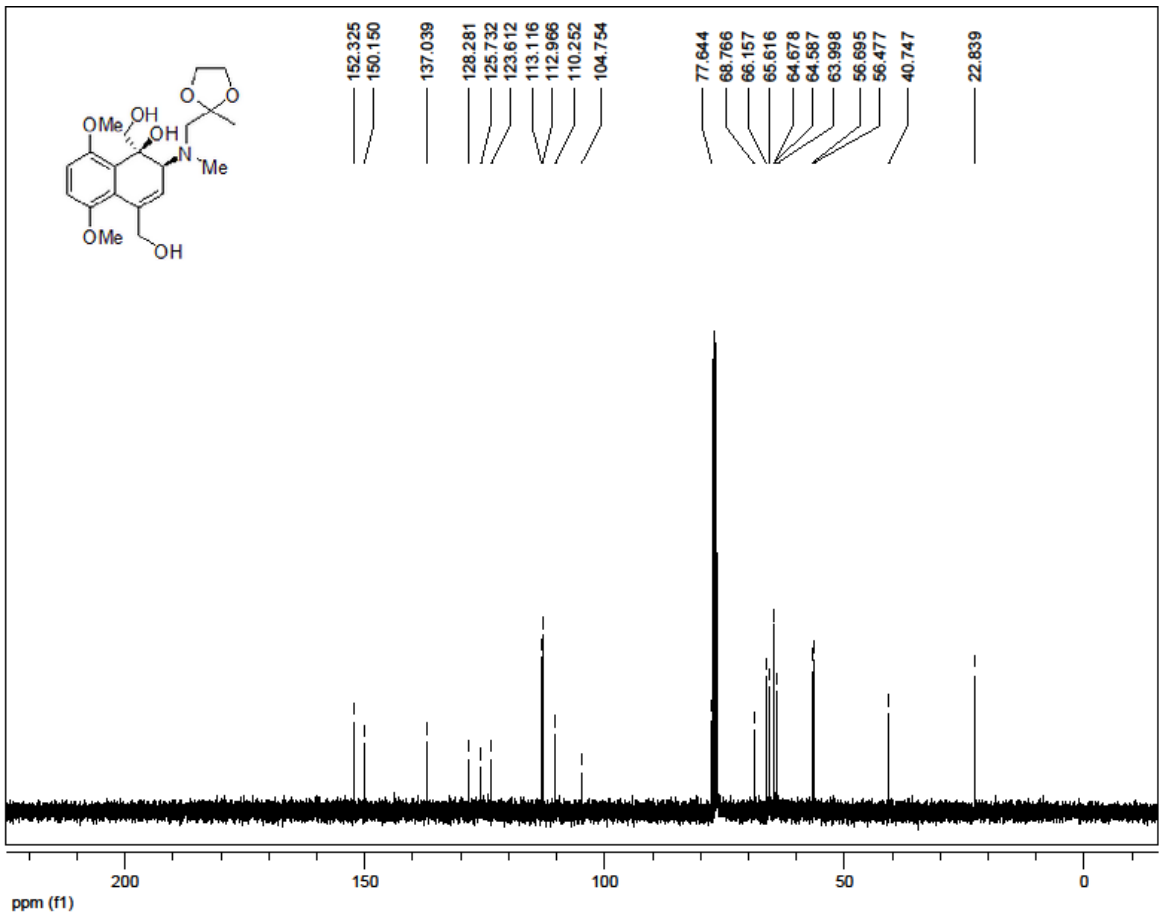
Cl
OTBS
6.900
6.817
4.721
4.691
4.522
4.491
0.910
0.123
0.103
1.80
1.83
1.17
1.15
9.14
6.26
10.0
5.0
0.0
ppm (t1)

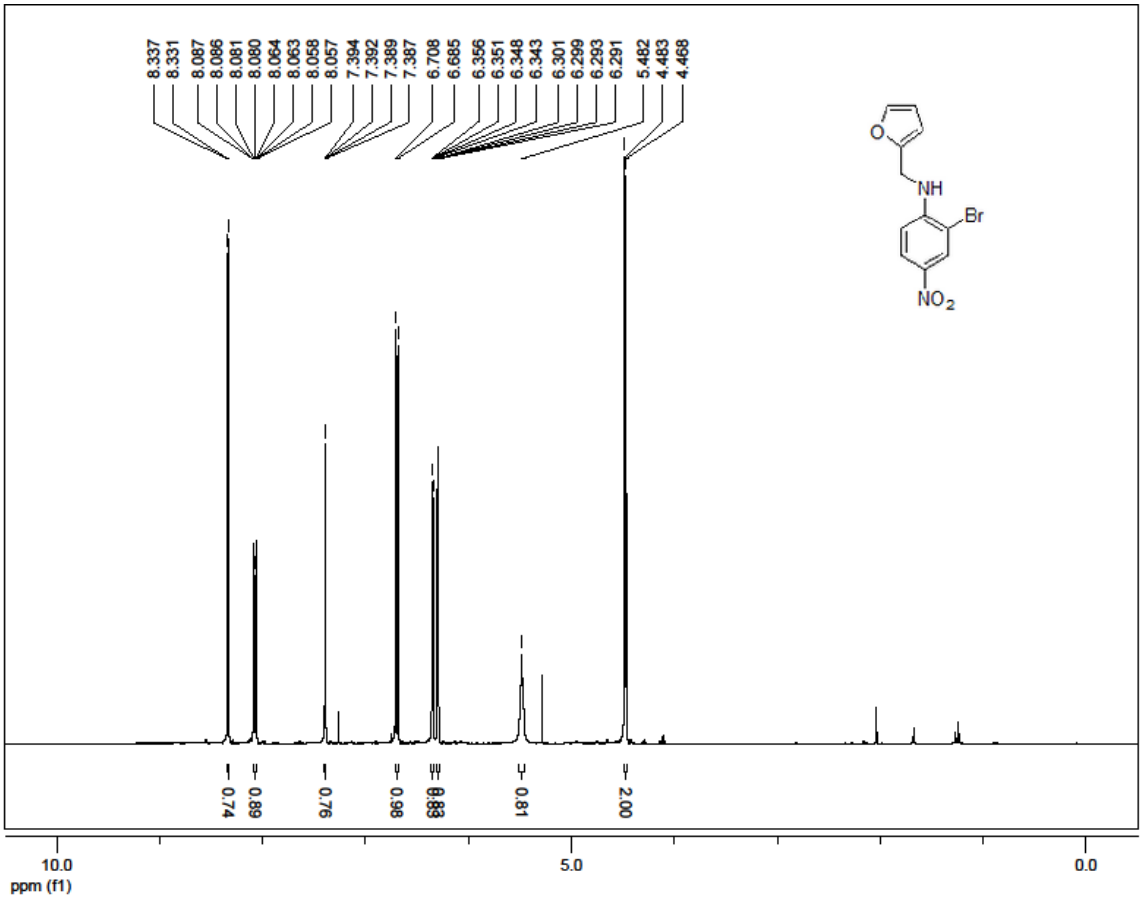

OTBS
Cl
O
Cl
OTBS
150.115
144.071
128.405
124.761
94.767
61.023
25.906
18.416
-5.148
-5.286
200
150
100
50
0
ppm (t1)

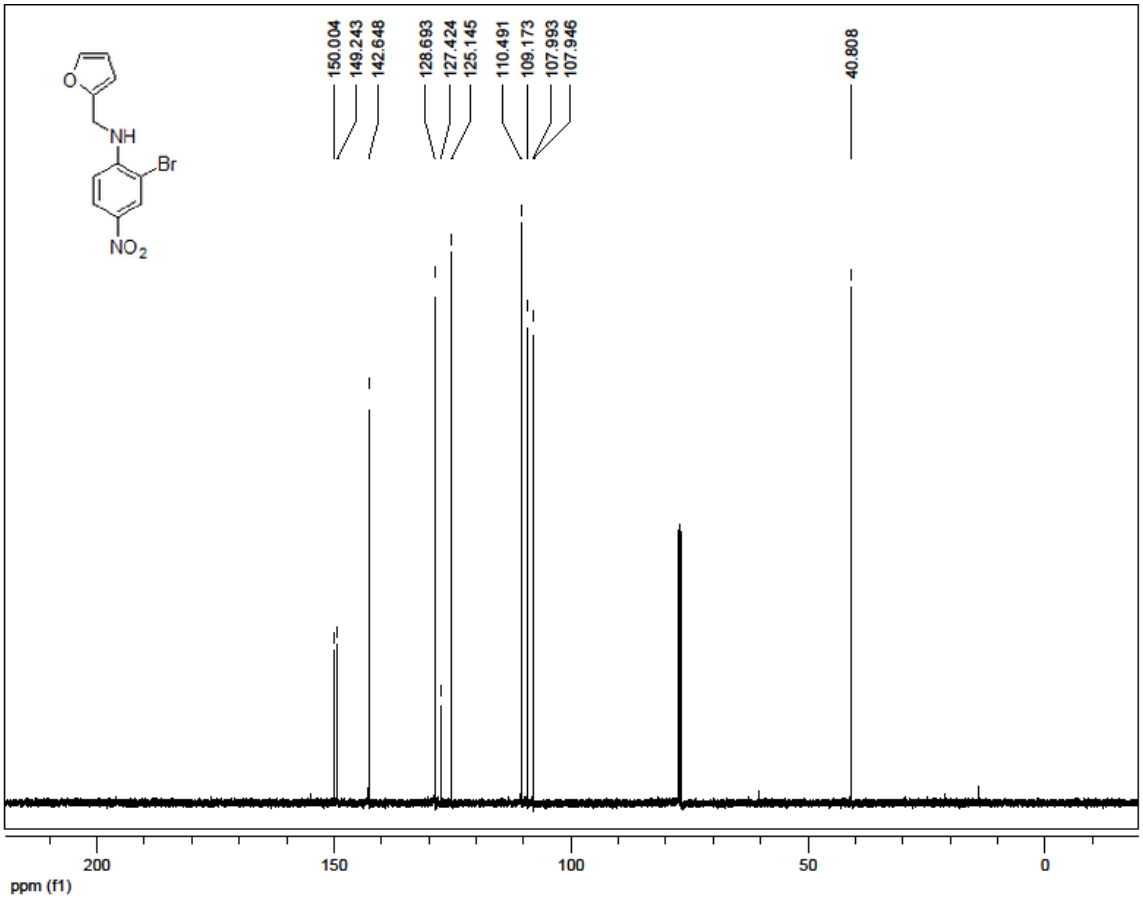

OMe
OTBS
O
OMe
OTBS
6.950
6.524
4.838
4.807
4.372
4.341
3.731
0.929
0.127
0.121
1.00
1.06
1.17
1.16
3.35
8.94
6.26
10.0
5.0
0.0
ppm (t1)


OMe
OTBS
O
OMe
OTBS
147.936
144.015
139.211
111.597
94.401
61.747
56.160
25.982
18.465
-4.978
-5.343
200
150
100
50
0
ppm (t1)

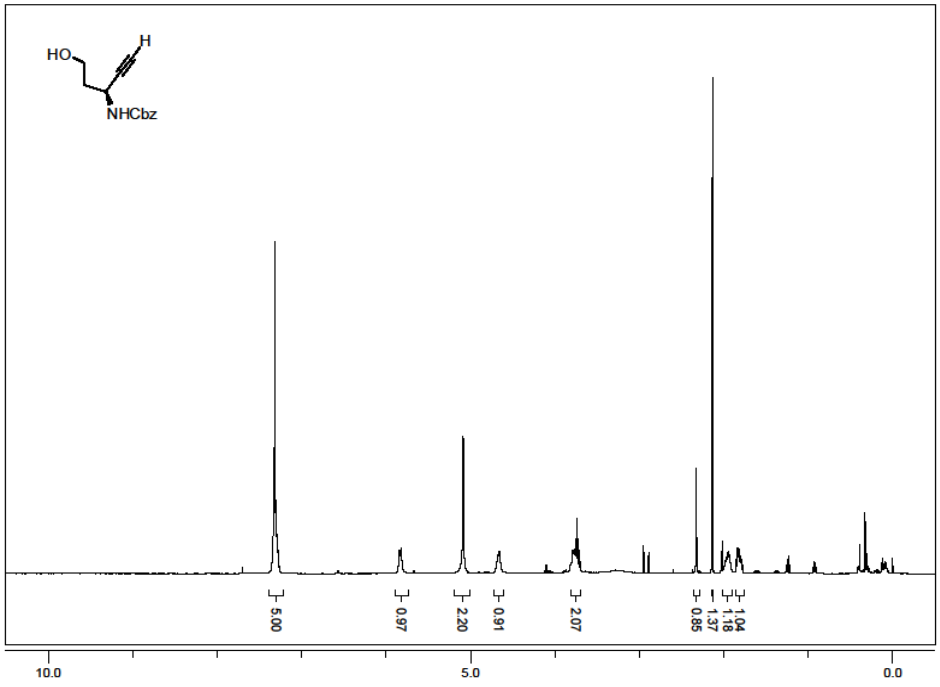

6.868
6.859
6.238
6.229
4.443
4.422
4.011
3.952
3.837
2.954
2.918
2.816
2.780
2.447
1.351
1.53
1.00
1.30
3.08
3.15
10.0
5.0
0.0
ppm (f1)
OMe
OH
OH
N
Me
OMe
OH

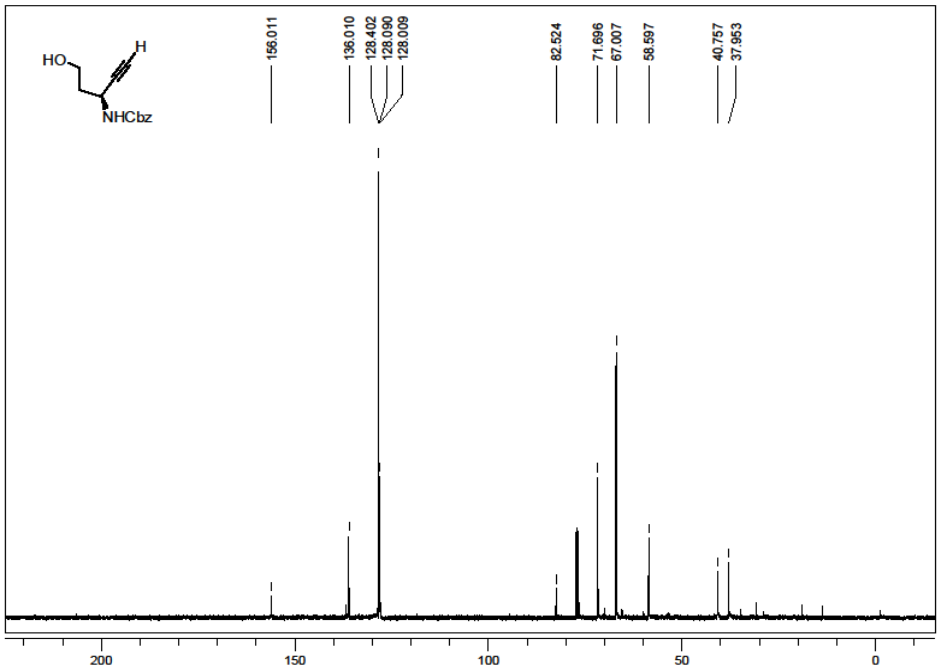

152.325
150.150
137.039
128.281
125.732
123.612
113.116
112.966
110.252
104.754
77.644
68.766
66.157
65.616
64.678
64.587
63.998
56.695
56.477
40.747
22.839
200
150
100
50
0
ppm (f1)
OMe
OH
OH
N
Me
OMe
OH

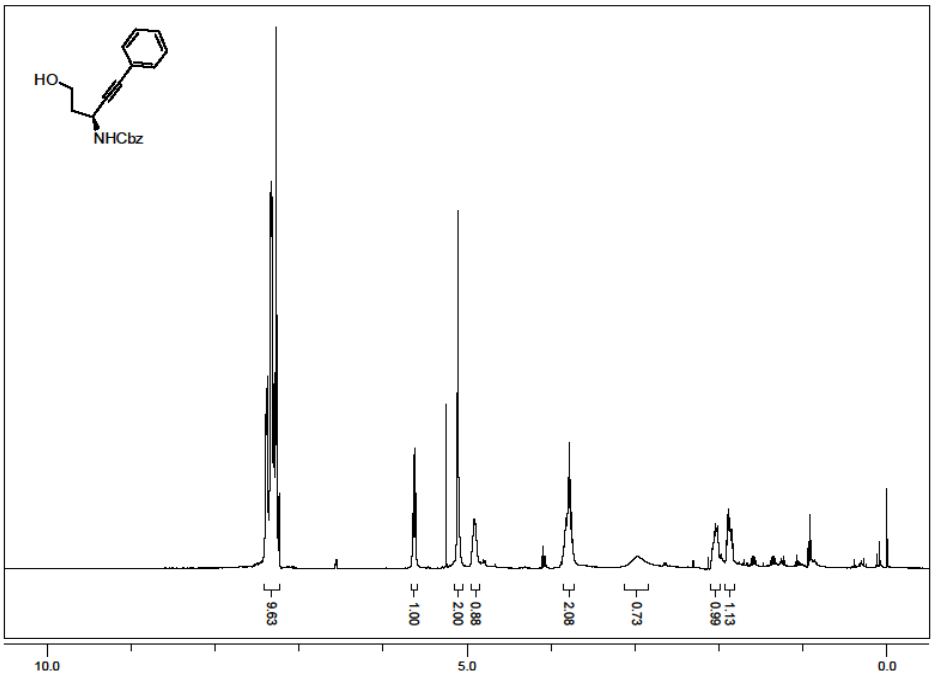

8.337
8.331
8.087
8.086
8.081
8.080
8.064
8.063
8.058
8.057
7.394
7.392
7.389
7.387
6.708
6.685
6.356
6.351
6.348
6.343
6.301
6.299
6.293
6.291
5.482
4.483
4.468
O
NH
Br
NO2
0.74
0.89
0.76
0.98
0.81
2.00
10.0
5.0
0.0
ppm (f1)

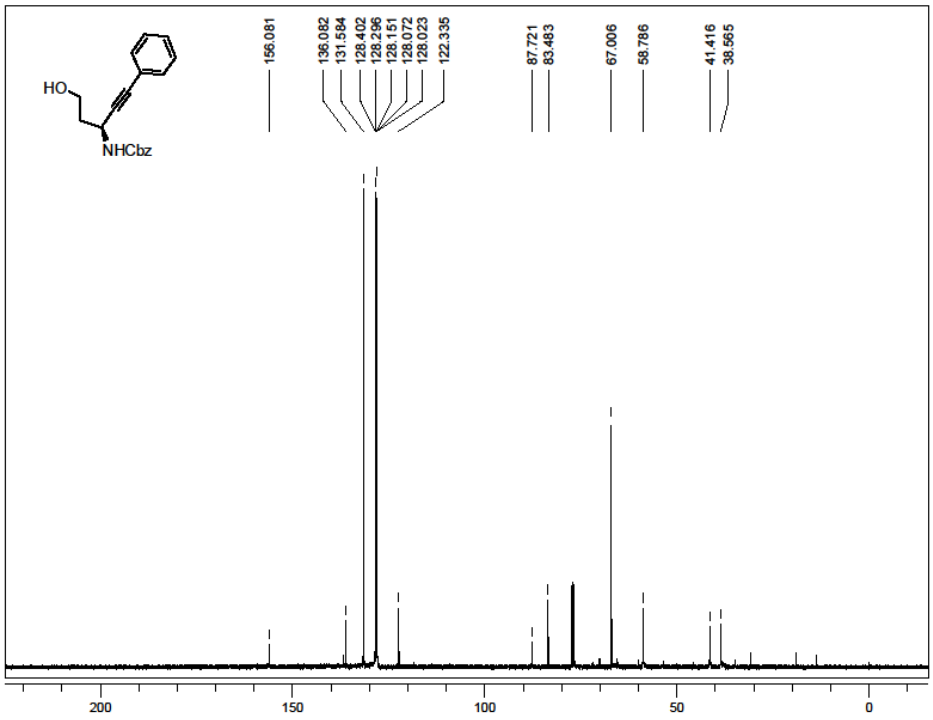

O
NH
Br
NO2
150.004
149.243
142.648
128.693
127.424
125.145
110.491
109.173
107.993
107.946
40.808
200
150
100
50
0
ppm (f1)

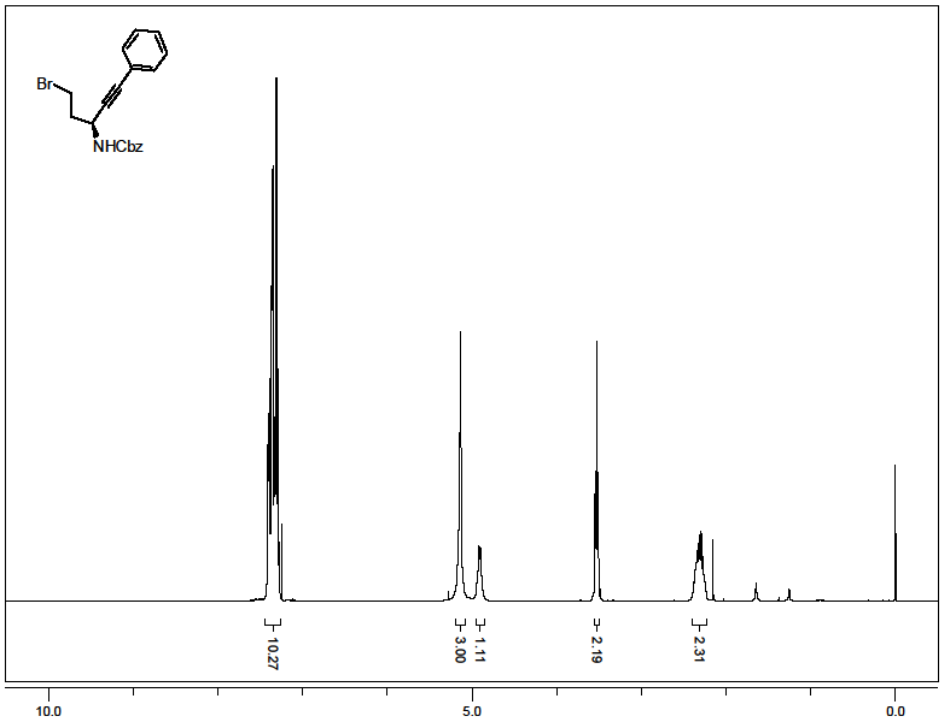
Chapter 2

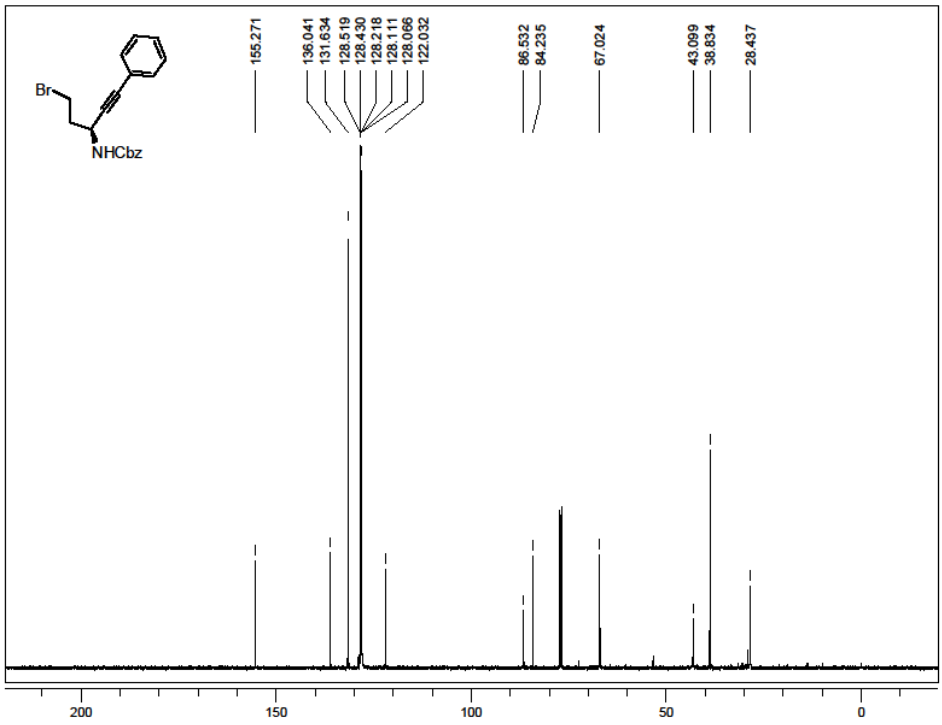

HO
H
NHCbz
5.00
0.97
2.20
0.91
2.07
0.85
1.37
1.18
1.04
10.0
5.0
0.0

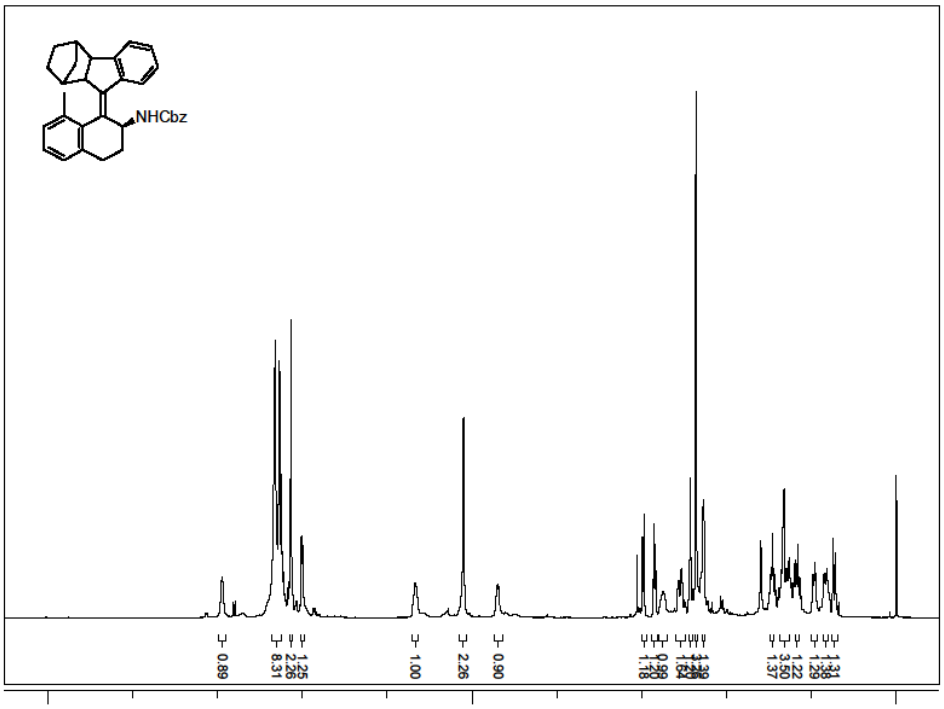

HO
H
NHCbz
156.011
136.010
128.402
128.090
128.009
82.524
71.696
67.007
58.597
40.757
37.953
200
150
100
50
0

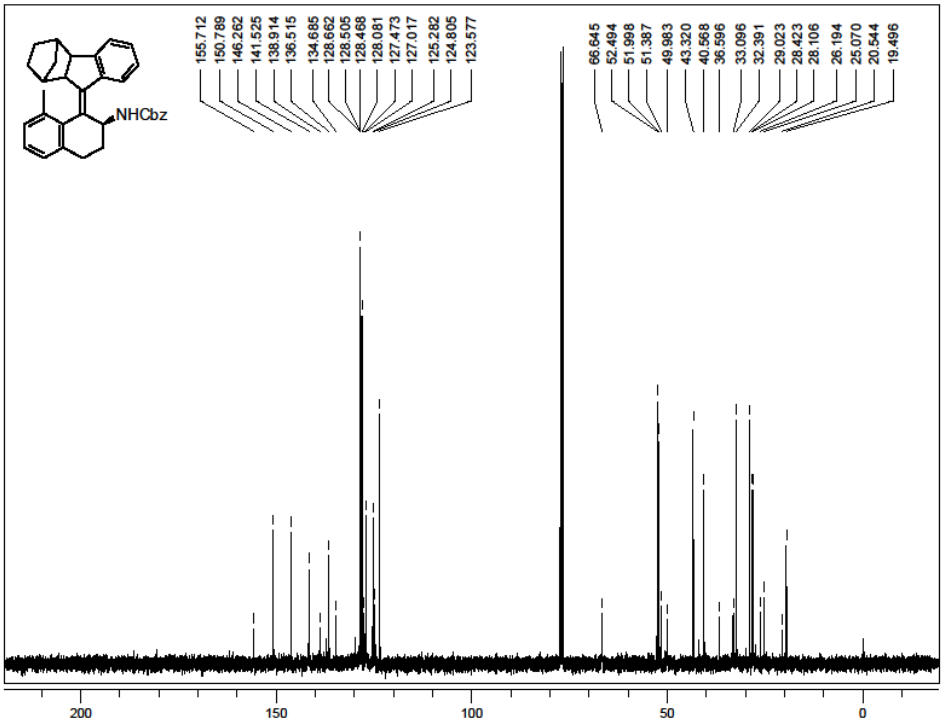

HO
NHCbz
0.93
1.00
2.00
0.88
2.08
0.73
0.99
1.13
10.0
5.0
0.0


HO
NHCbz
156.081
136.082
131.584
128.402
128.296
128.151
128.072
128.023
122.335
87.721
83.483
67.006
58.786
41.416
38.565
200
150
100
50
0

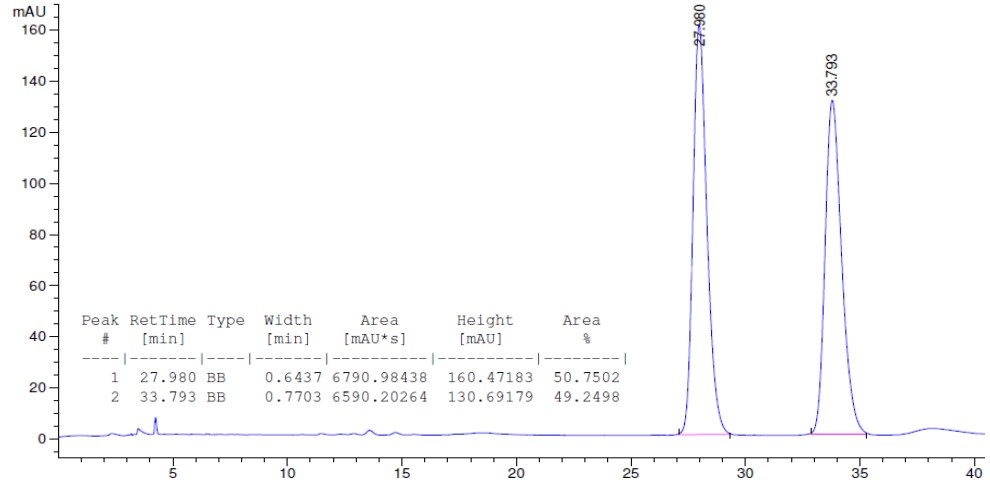

Br
NHCbz
10.27
3.00
1.11
2.19
2.31
10.0
5.0
0.0

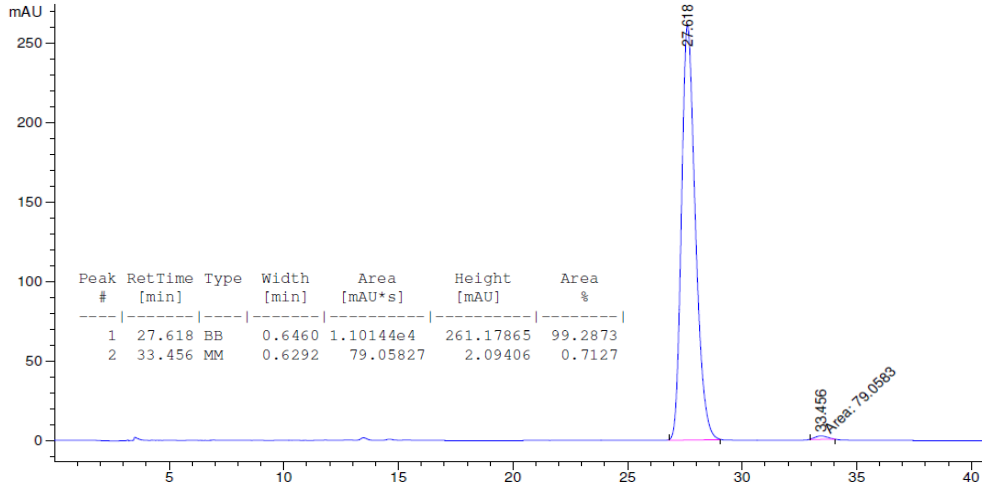

Br
NHCbz
155.271
136.041
131.634
128.519
128.430
128.218
128.111
128.066
122.032
86.532
84.235
67.024
43.099
38.834
28.437
200
150
100
50
0

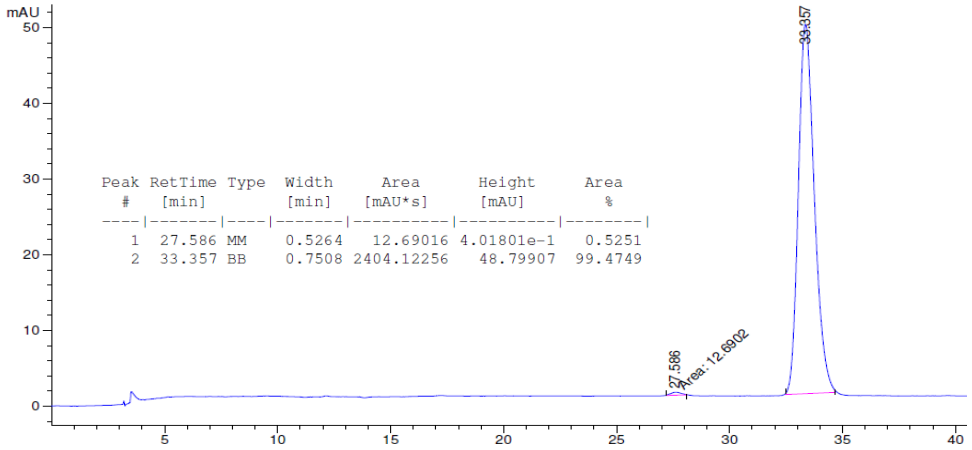

NHCbz
0.89
8.31
2.25
2.26
1.00
2.26
0.90
1.18
0.99
1.37
3.50
1.22
1.29
1.31
1.39
10.0
5.0
0.0


NHCbz
155.712
150.789
146.262
141.525
138.914
136.515
134.685
128.662
128.505
128.468
128.081
127.473
127.017
125.282
124.805
123.577
66.645
52.494
51.998
51.387
49.983
43.320
40.568
36.596
33.096
32.391
29.023
28.423
28.106
26.194
25.070
20.544
19.496
200
150
100
50
0

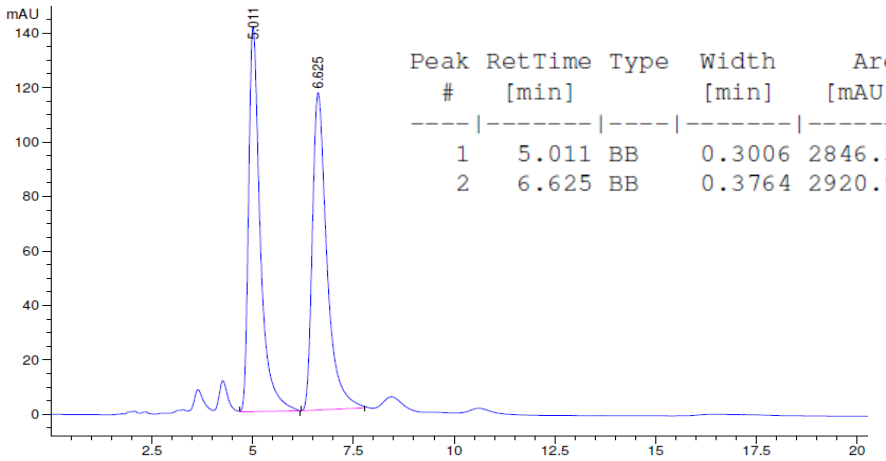
HPLC trace of rac-**2.041b**, (S)-**2.041b**, and (R)-**2.041b**



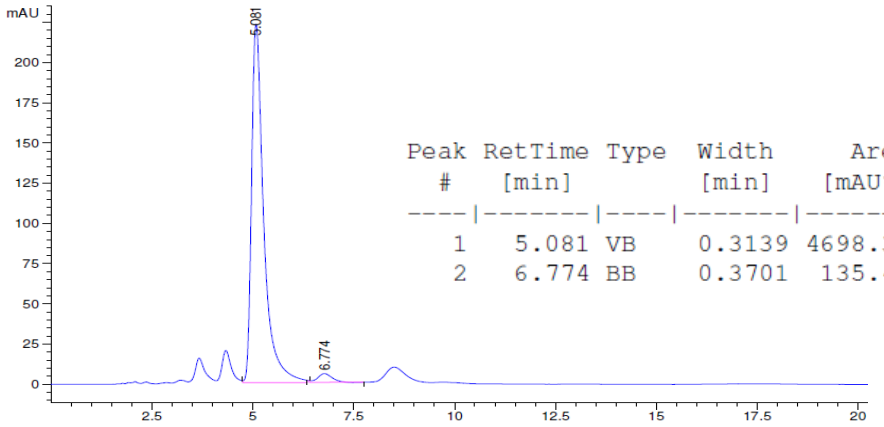




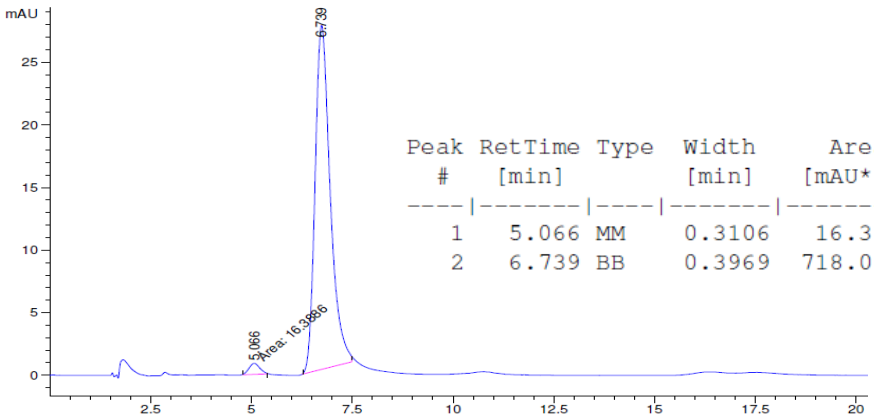
HPLC trace of rac-**2.042b**, (S)-**2.042b**, and (R)-**2.042b**



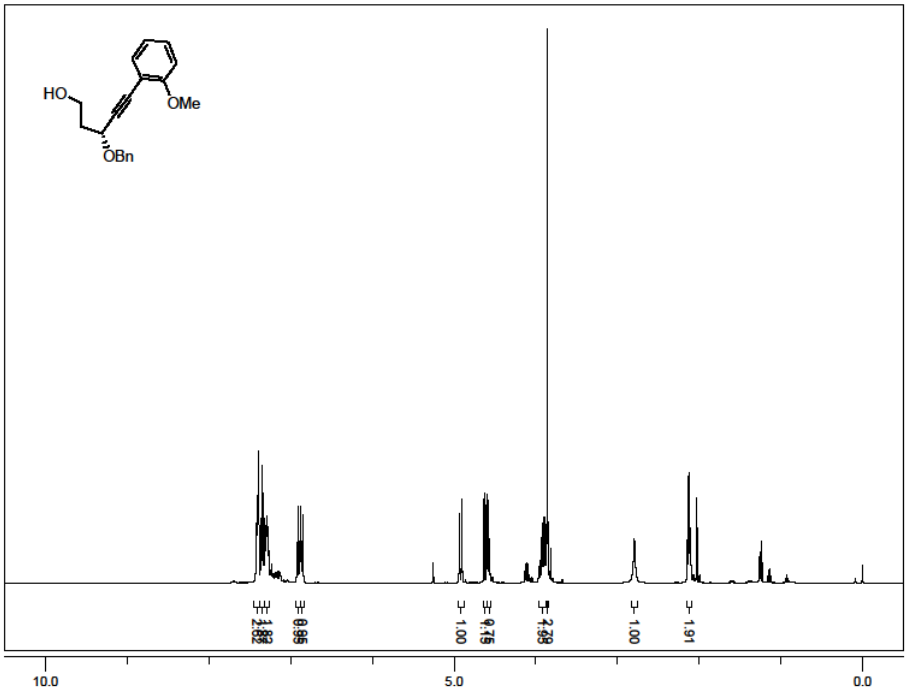
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.011	BB	0.3006	2846.35937	141.56934	49.3536
2	6.625	BB	0.3764	2920.92041	116.52809	50.6464

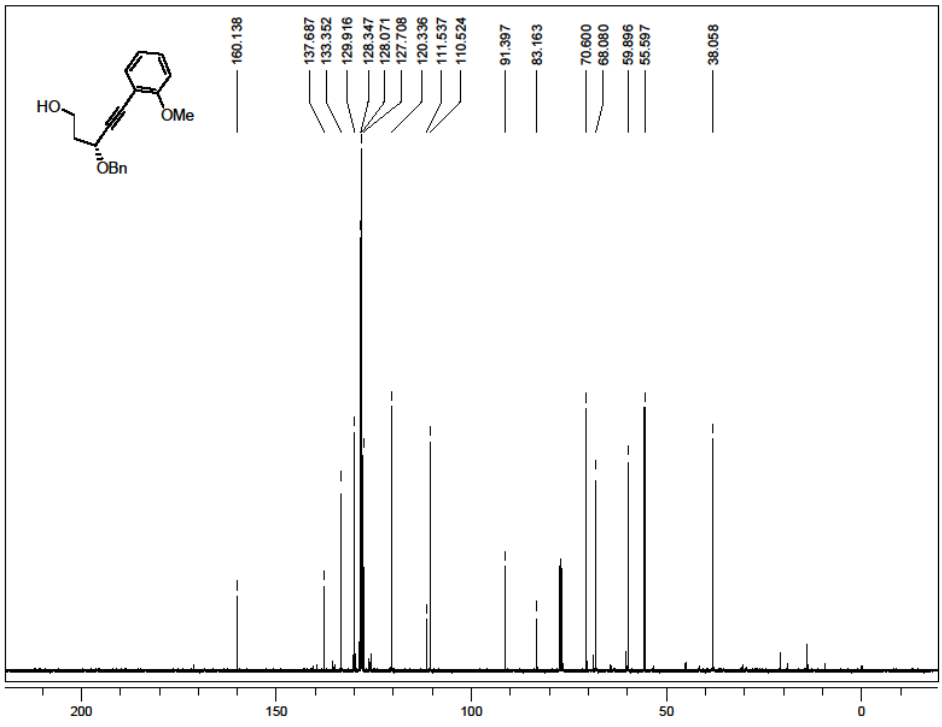


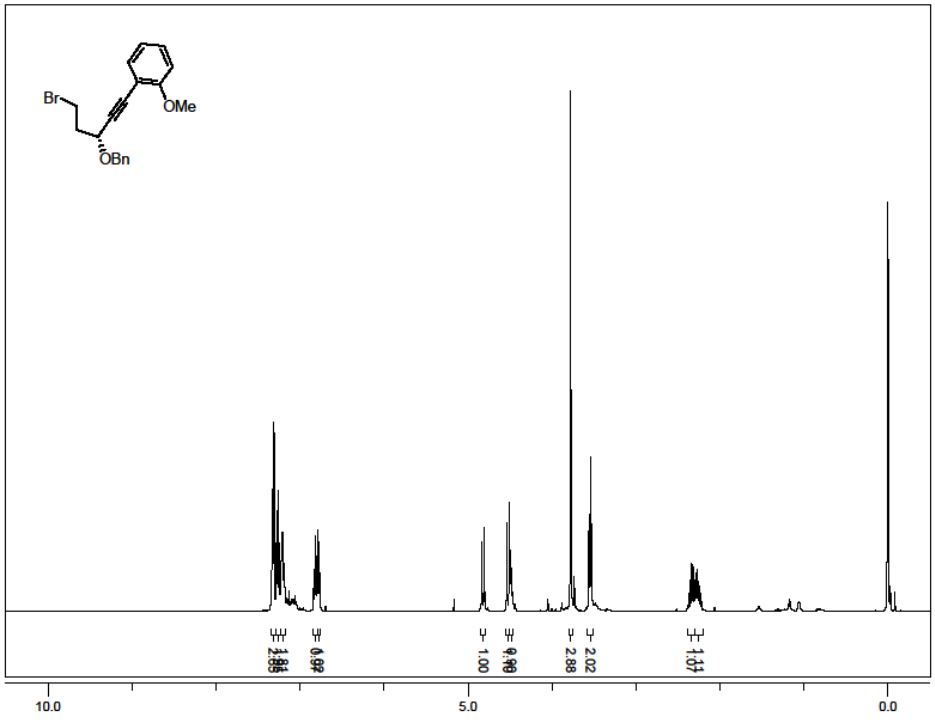
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.081	VB	0.3139	4698.32715	222.92935	97.1983
2	6.774	BB	0.3701	135.42508	5.48362	2.8017

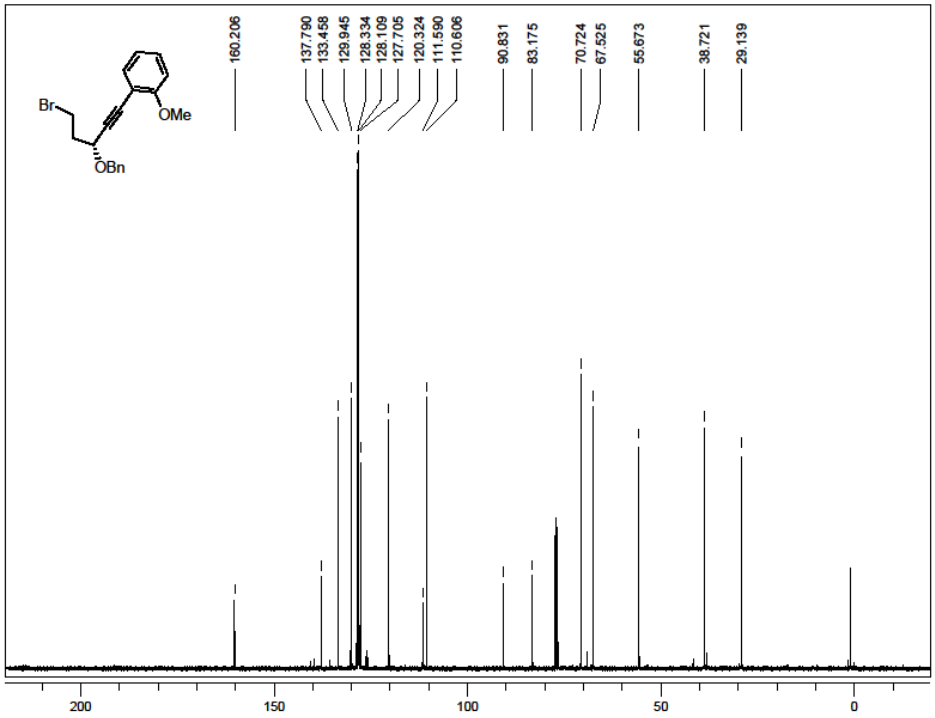


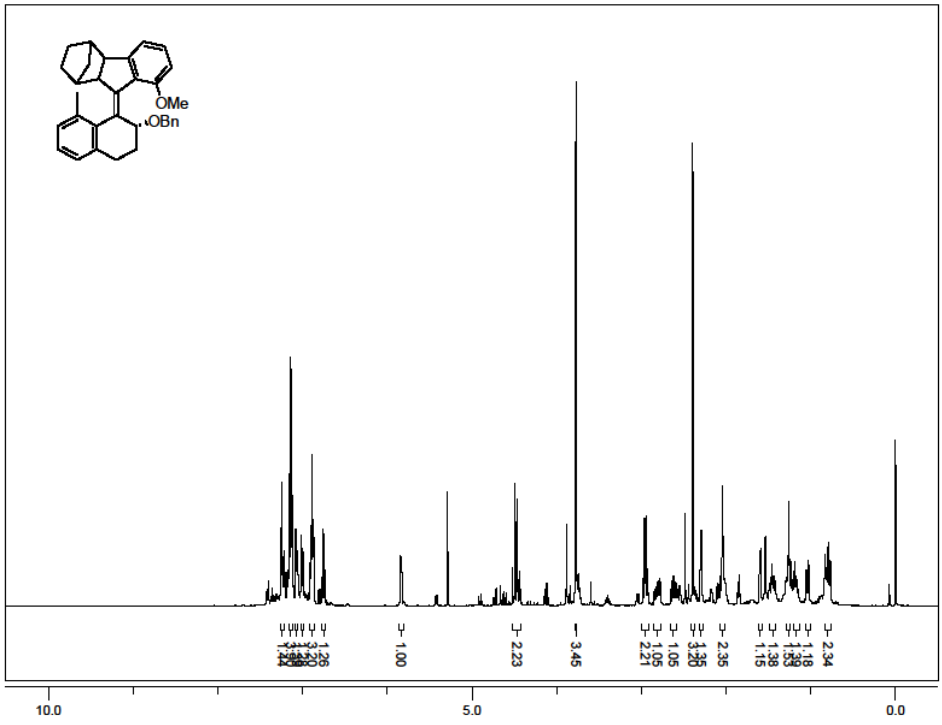
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.066	MM	0.3106	16.38861	8.79379e-1	2.2313
2	6.739	BB	0.3969	718.09088	27.48118	97.7687

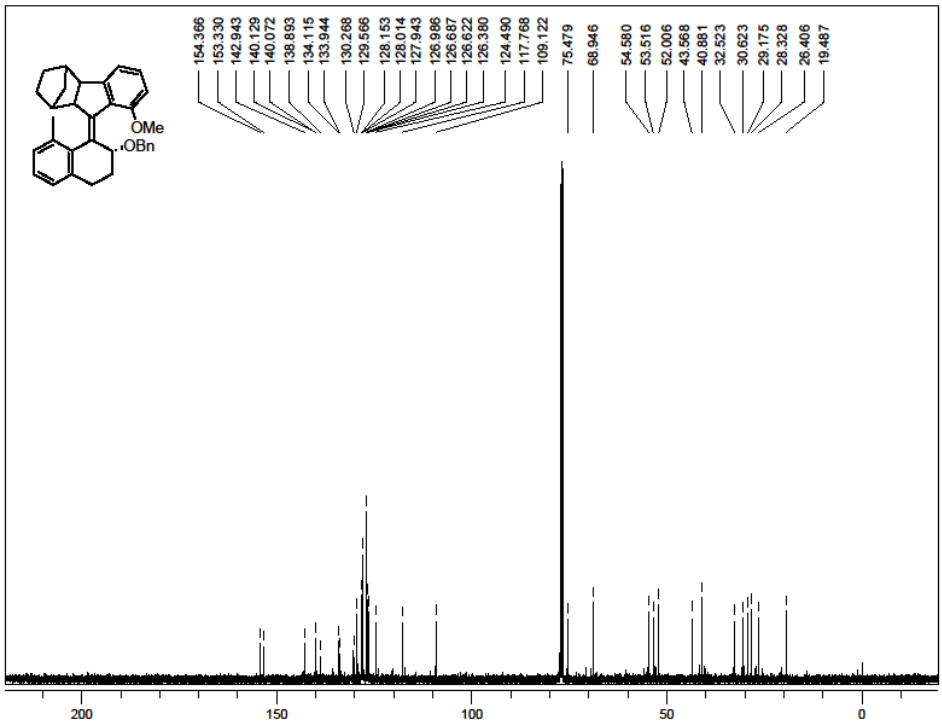

HO
OMe
OBn
1.00
0.75
2.29
1.00
1.91
10.0
5.0
0.0

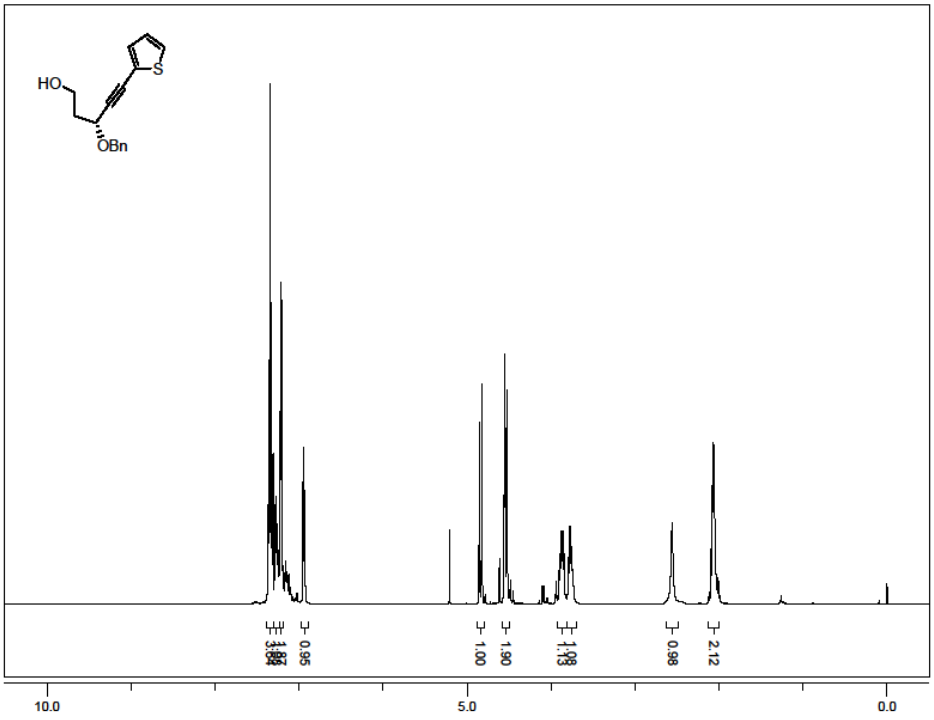

HO
OMe
OBn
160.138
137.687
133.352
129.916
128.347
128.071
127.708
120.336
111.537
110.524
91.397
83.163
70.600
68.080
59.896
55.597
38.058
200
150
100
50
0

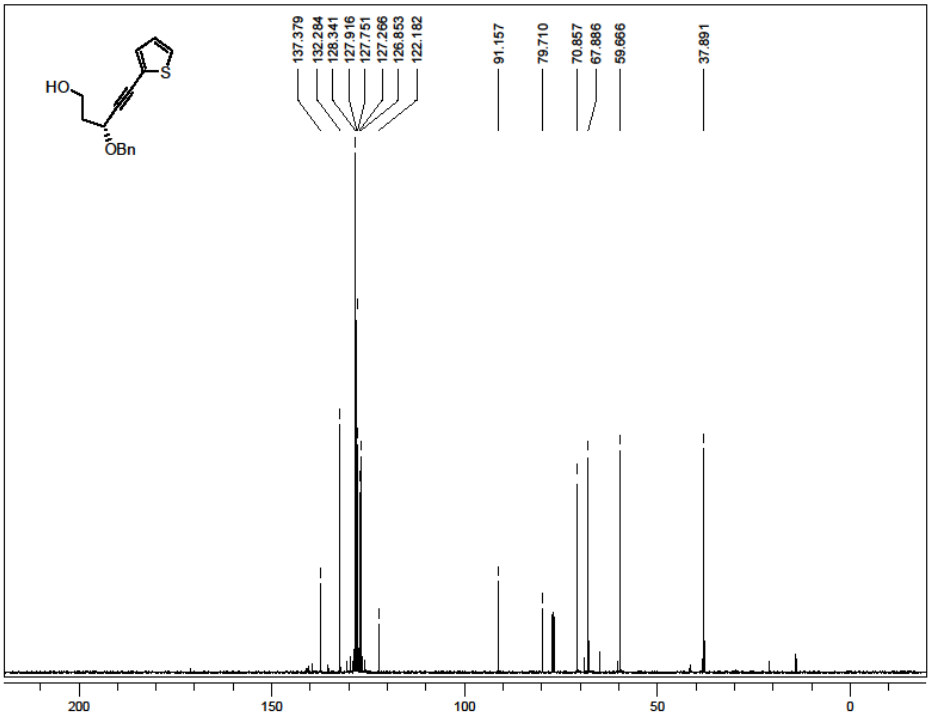

Br
OMe
OBn
1.00
0.98
2.88
2.02
1.17
10.0
5.0
0.0

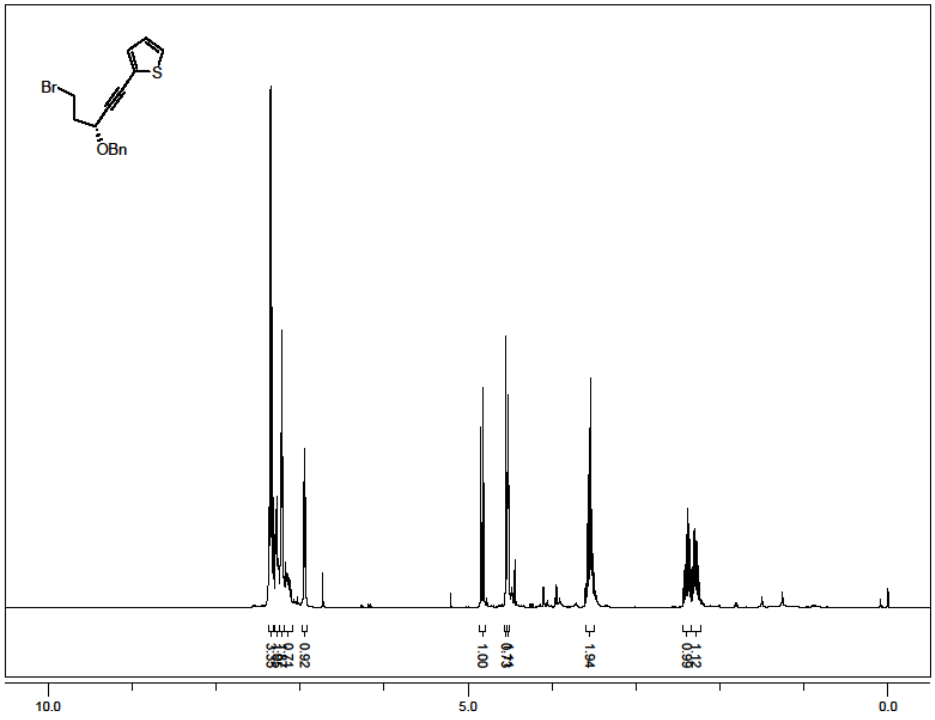

Br
OMe
OBn
160.206
137.790
133.458
129.945
128.334
128.109
127.705
120.324
111.590
110.606
90.831
83.175
70.724
67.525
55.673
38.721
29.139
200
150
100
50
0

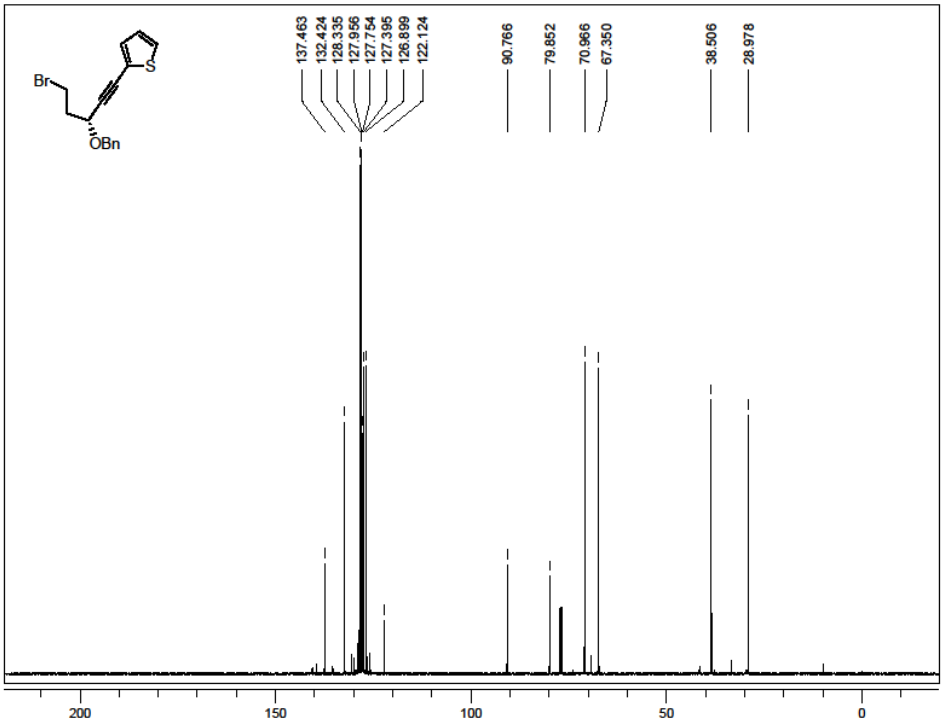

OMe
OBn
1.00
2.23
3.45
2.21
1.05
1.05
3.20
2.35
1.15
1.38
1.39
1.53
1.18
2.34
10.0
5.0
0.0


OMe
OBn
154.366
153.330
142.943
140.129
140.072
138.893
134.115
133.944
130.268
129.566
128.153
128.014
127.943
126.986
126.687
126.622
126.380
124.490
117.768
109.122
75.479
68.946
54.580
53.516
52.006
43.568
40.881
32.523
30.623
29.175
28.328
26.406
19.487
200
150
100
50
0


HO
S
OBn
0.96
1.00
1.90
1.88
0.98
2.12
10.0
5.0
0.0


HO
S
OBn
137.379
132.264
128.341
127.916
127.751
127.266
126.853
122.182
91.157
79.710
70.857
67.886
59.666
37.891
200
150
100
50
0


Br
S
OBn
0.92
1.00
0.71
1.94
1.12
0.99
10.0
5.0
0.0


Br
S
OBn
137.463
132.424
128.335
127.956
127.754
127.395
126.899
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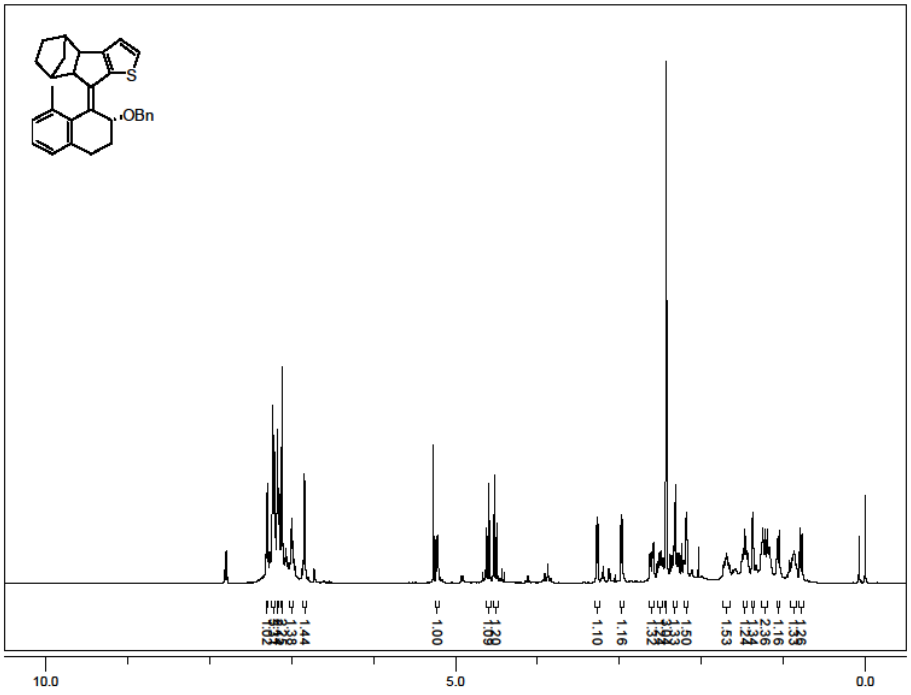
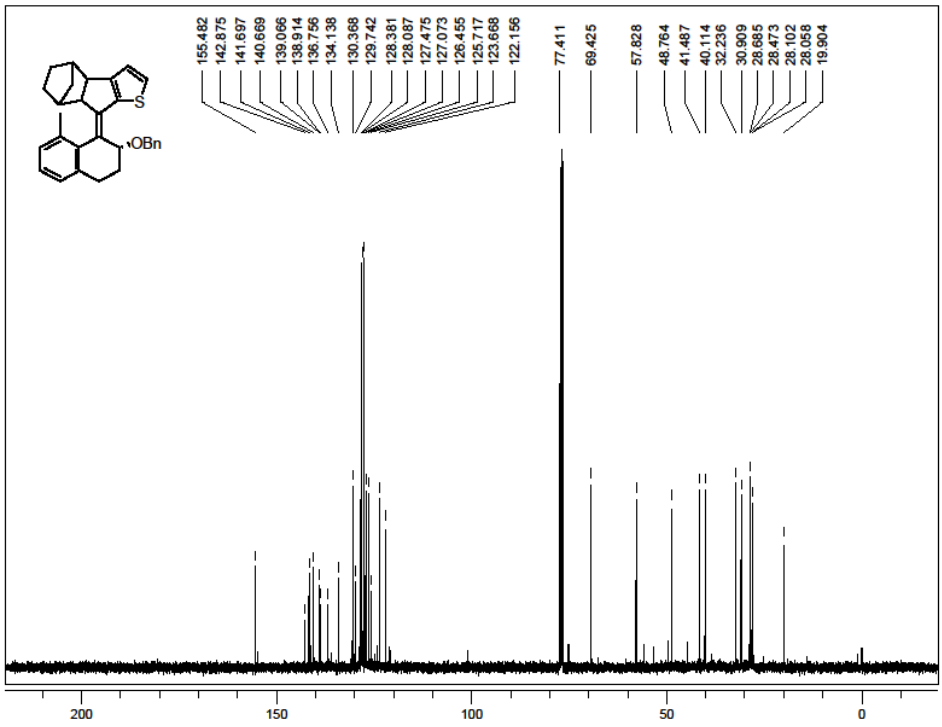
90.766
79.852
70.966
67.350
38.506
28.978
200
150
100
50
0


S
OBn
1.00
1.10
1.16
1.53
10.0
5.0
0.0


155.482
142.875
141.697
140.669
139.066
138.914
136.756
134.138
130.368
129.742
128.381
128.087
127.475
127.073
126.455
125.717
123.668
122.156
77.411
69.425
57.828
48.764
41.487
40.114
32.236
30.909
28.685
28.473
28.102
28.058
19.904
S
OBn
200
150
100
50
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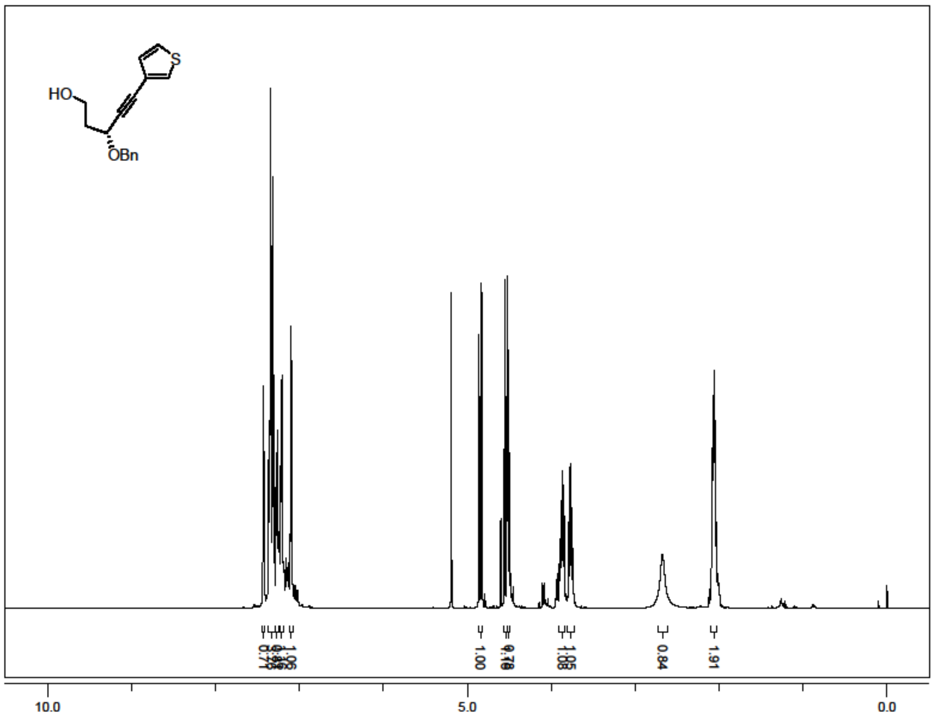
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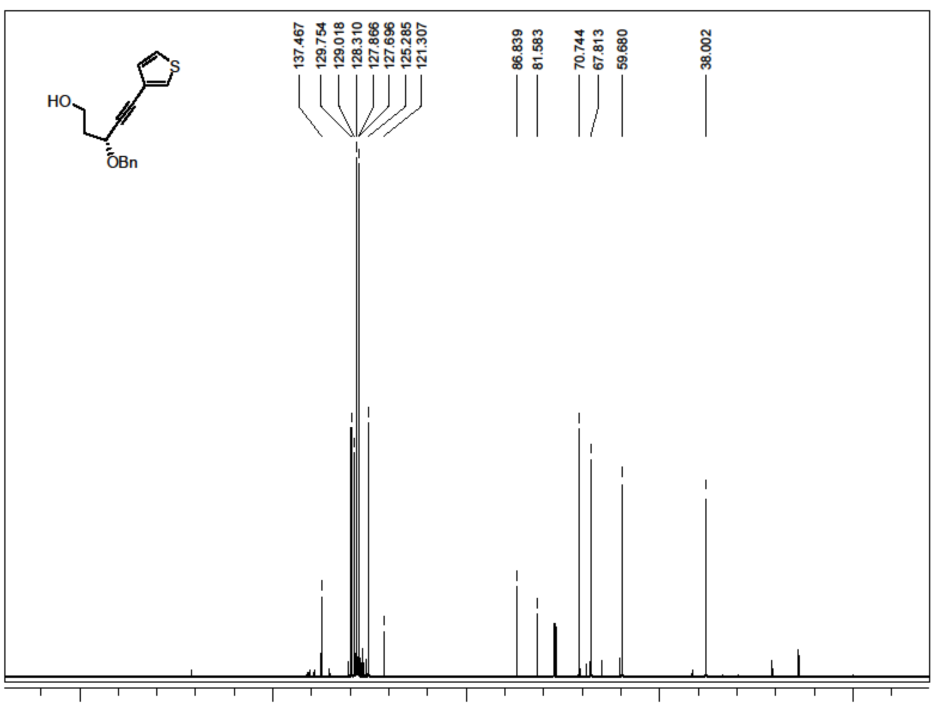
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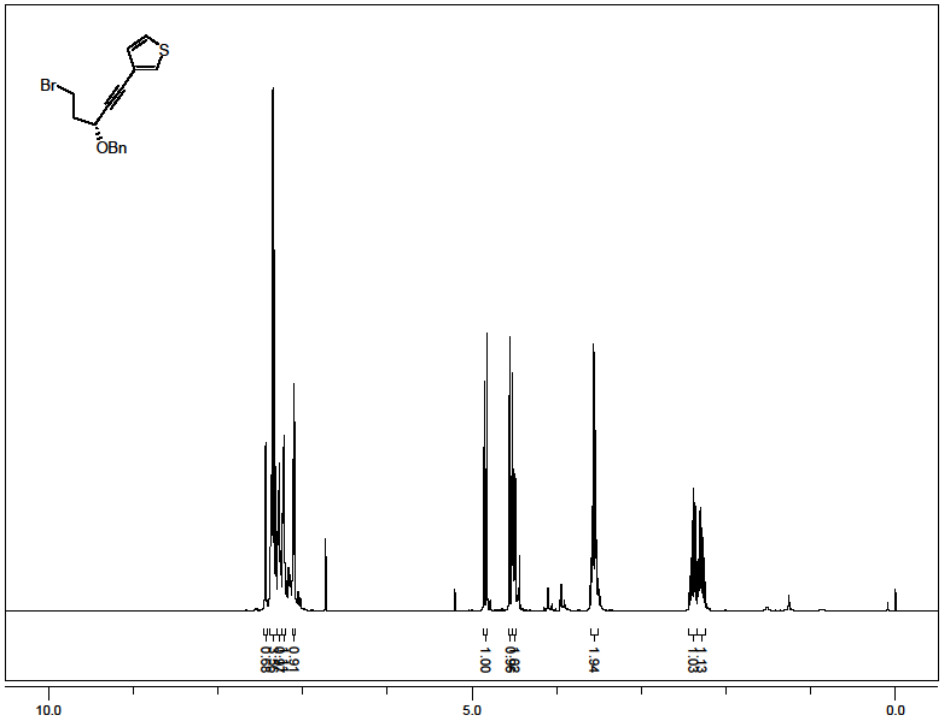
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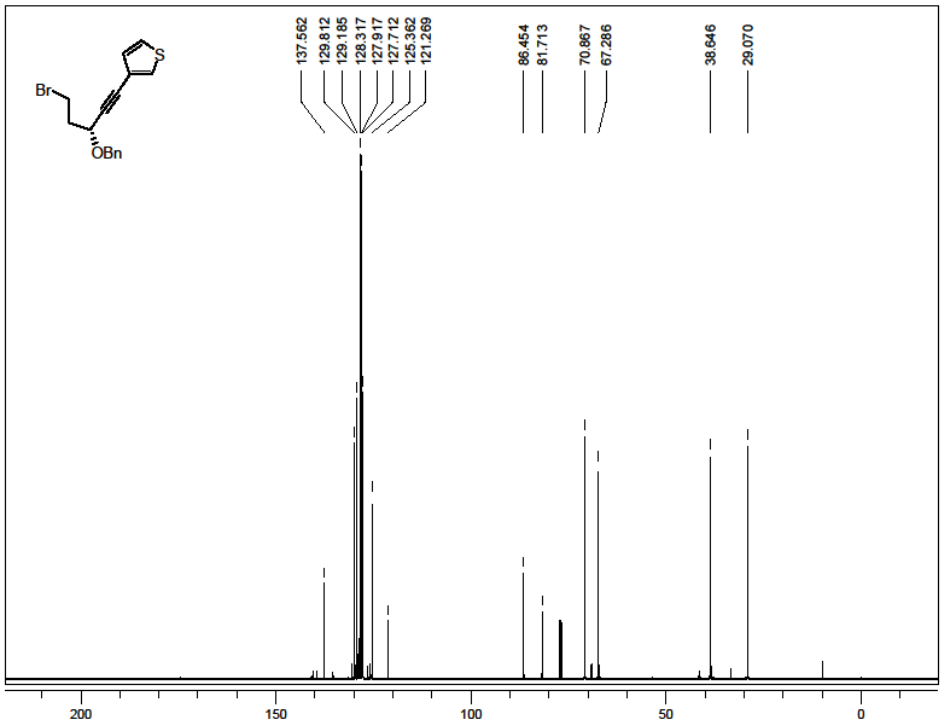
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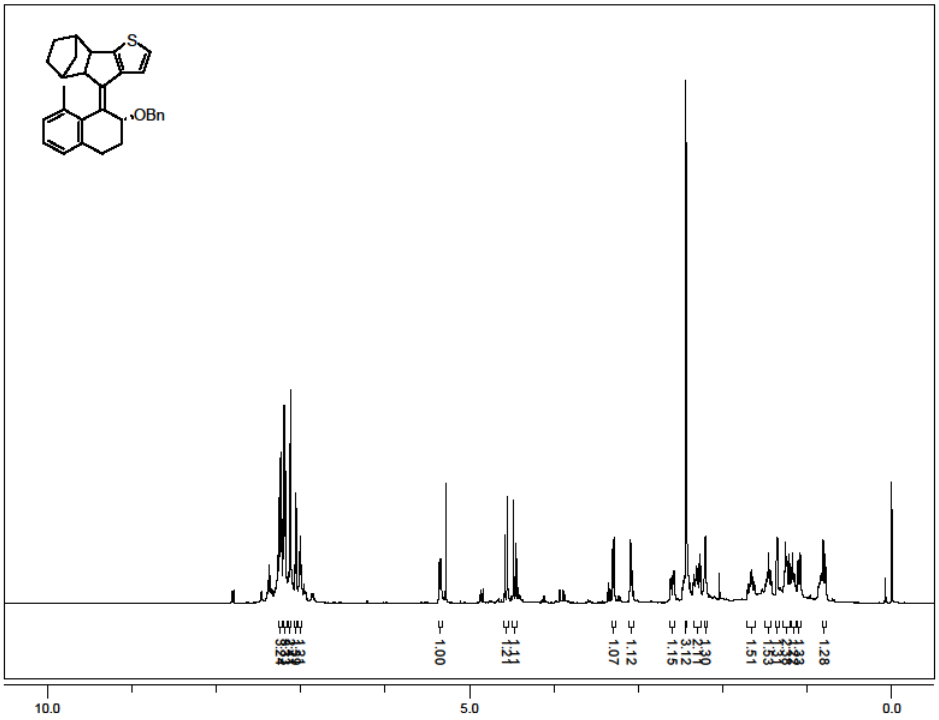
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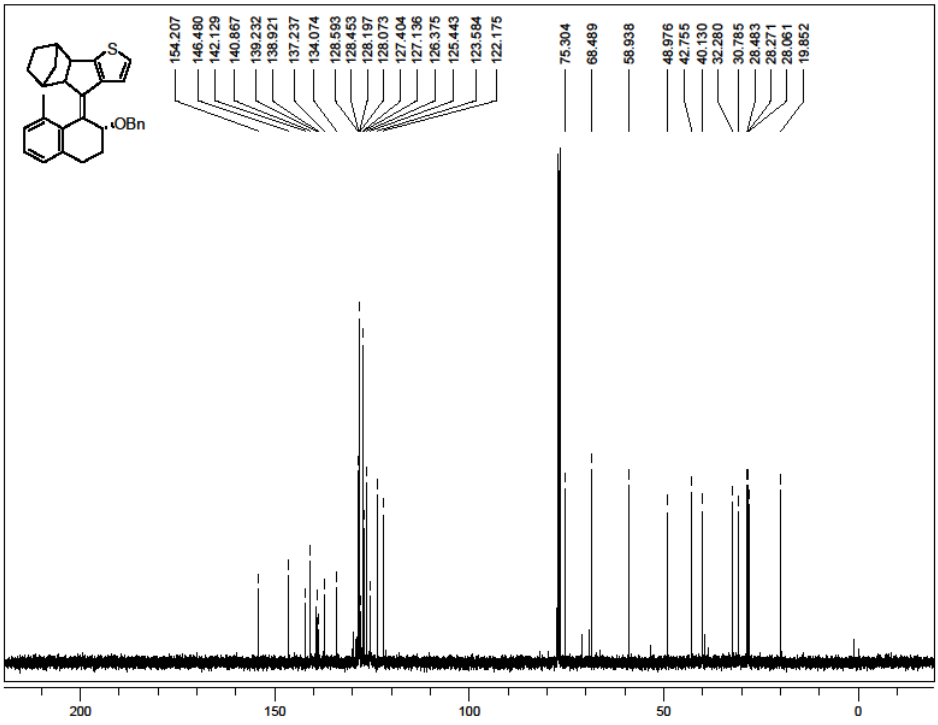
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128.073
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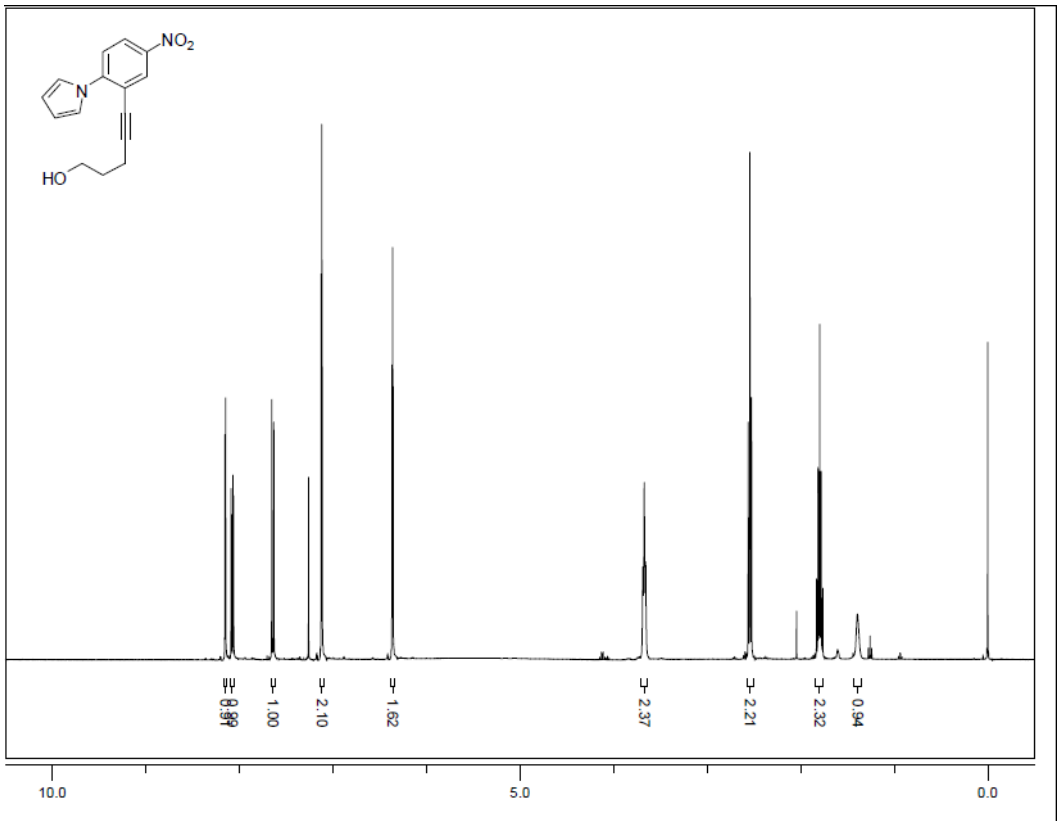
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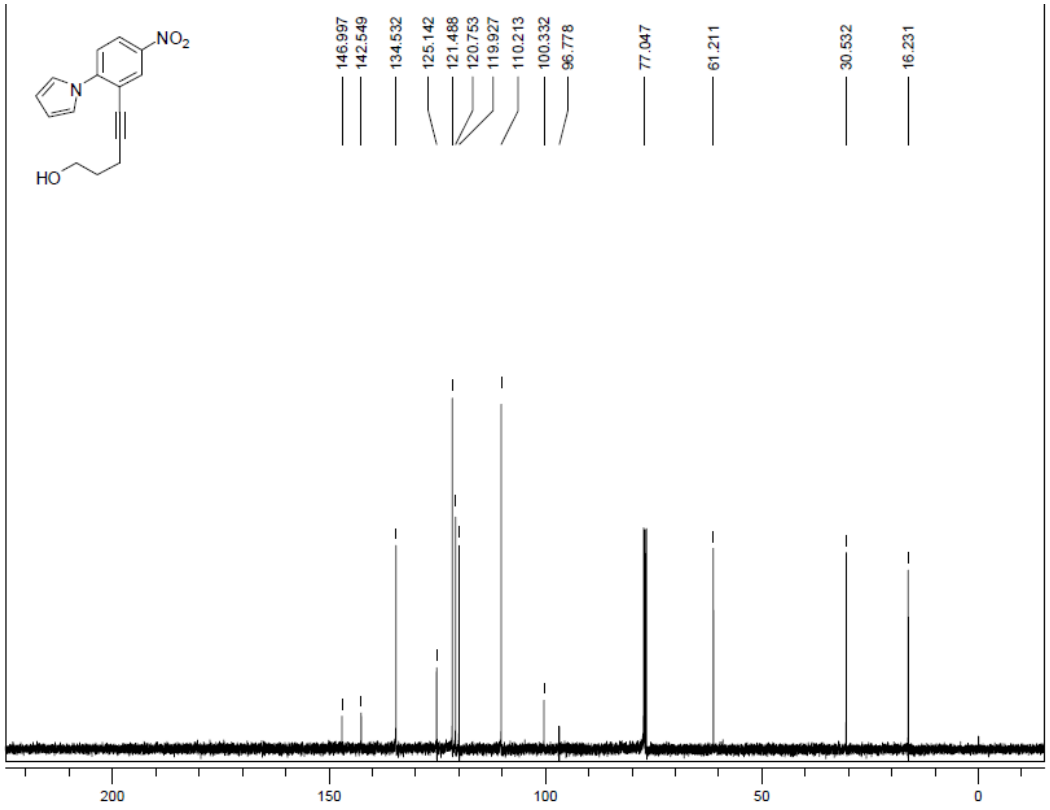
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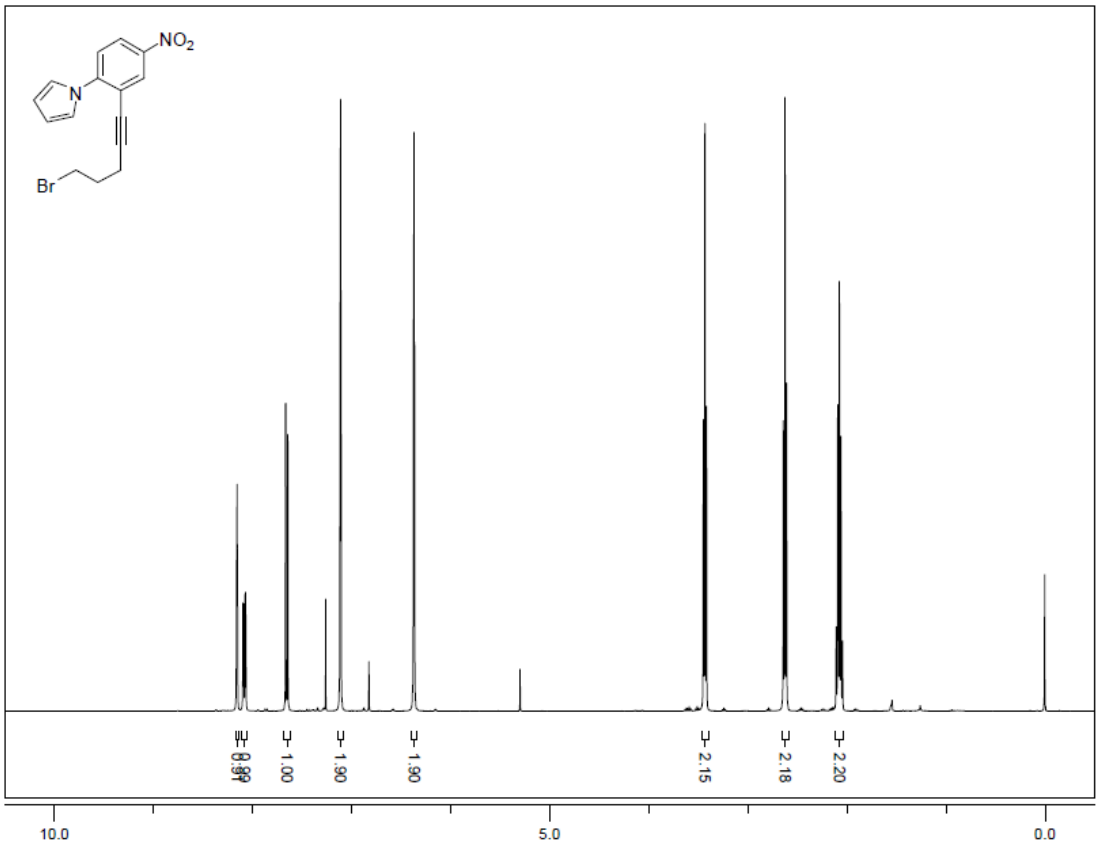
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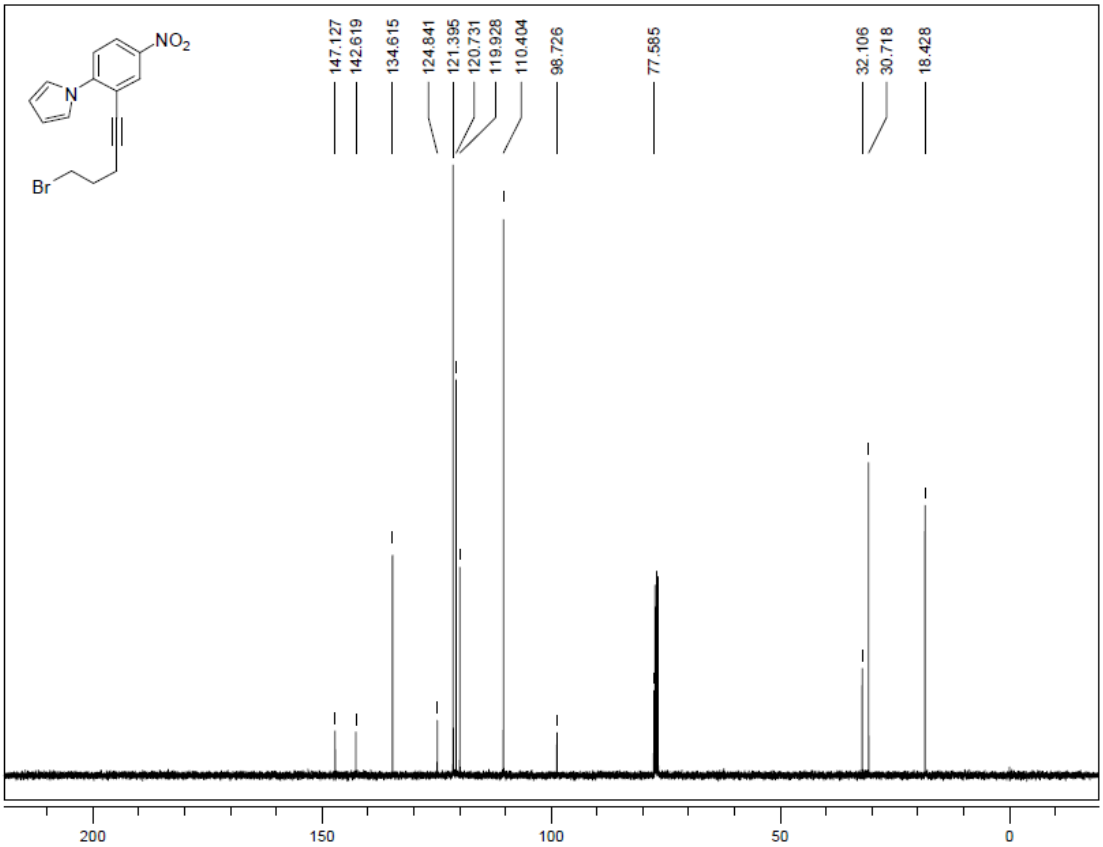
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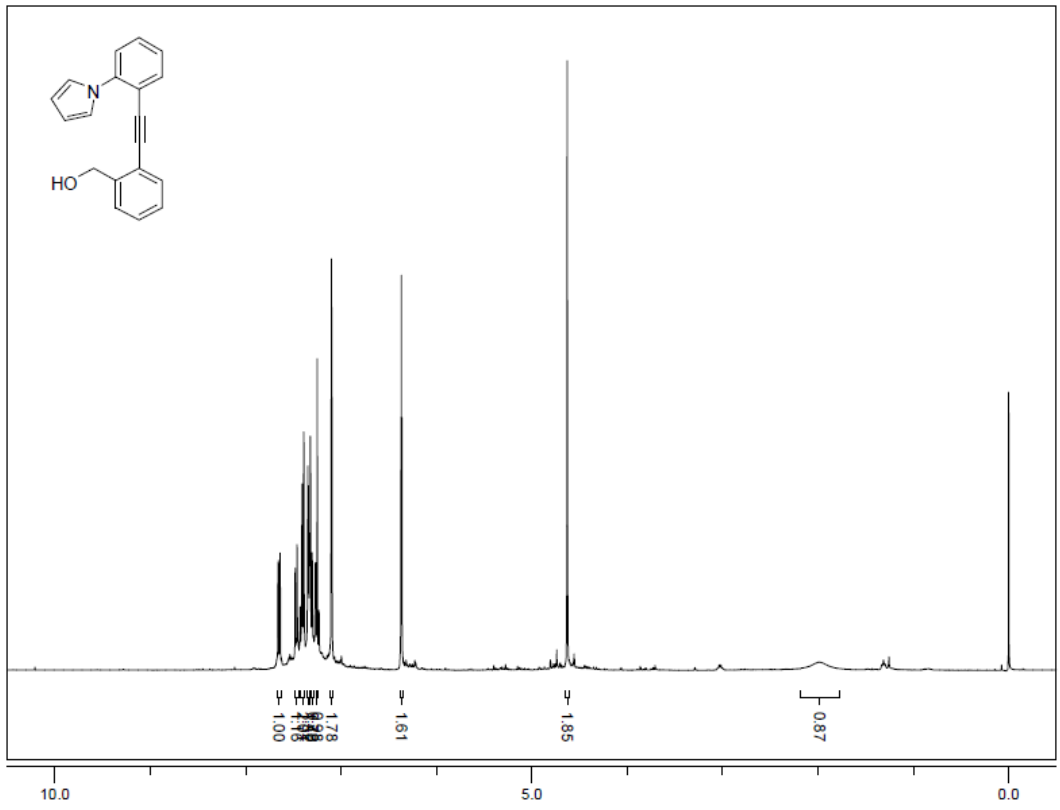
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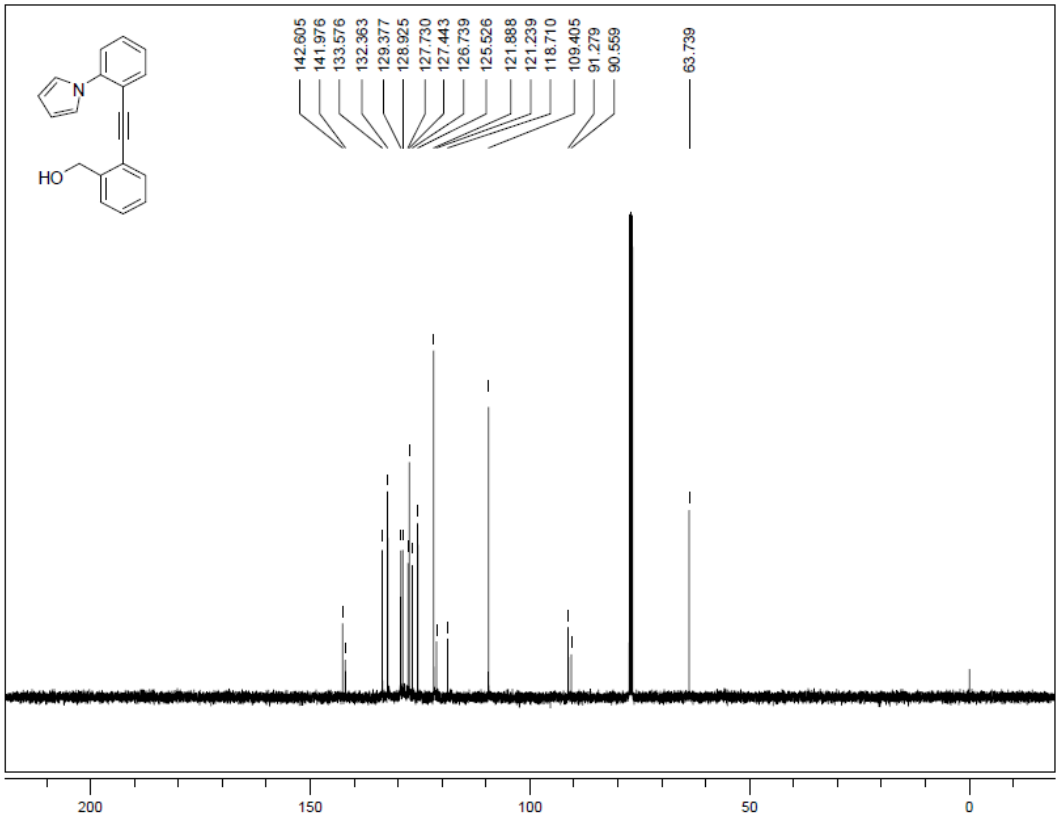
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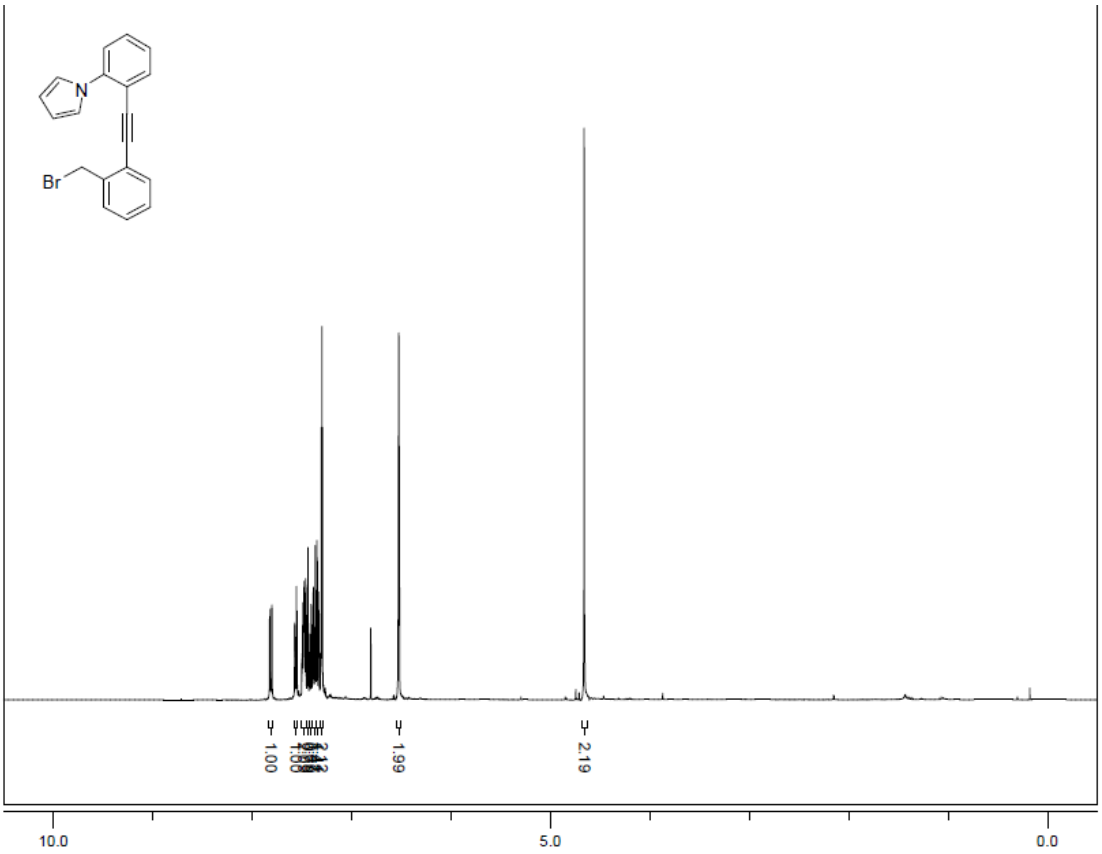
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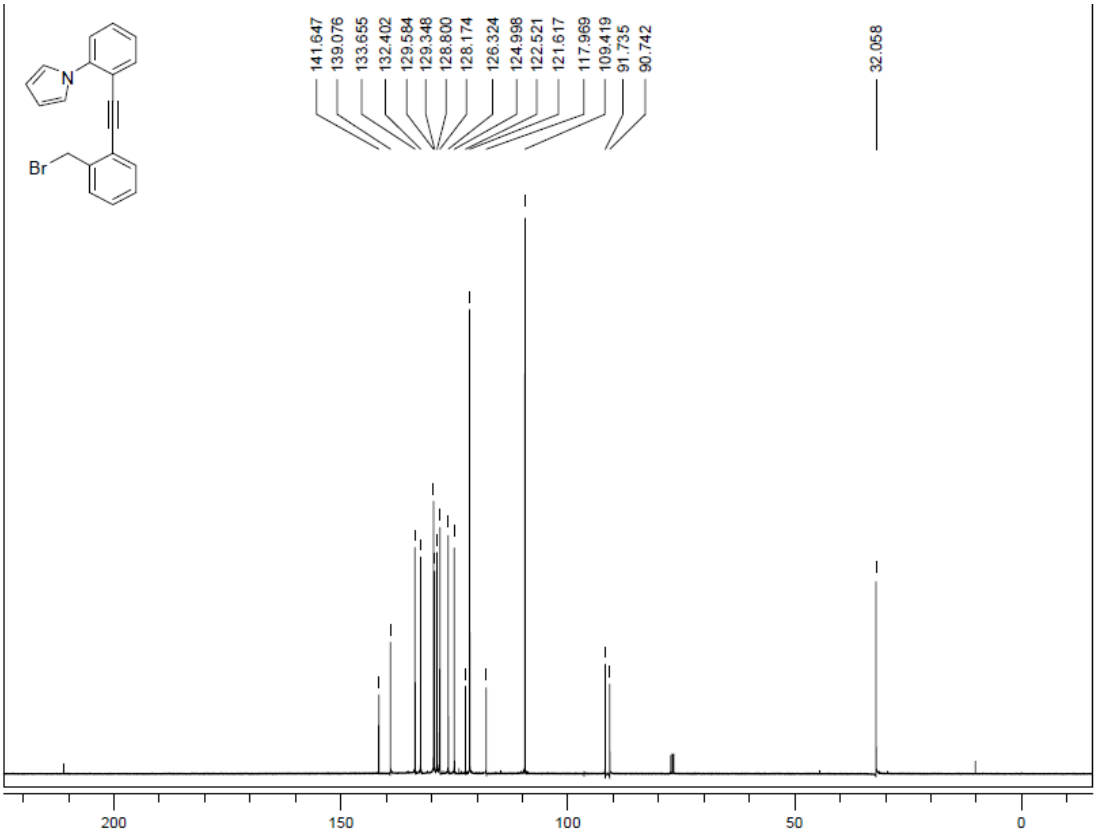
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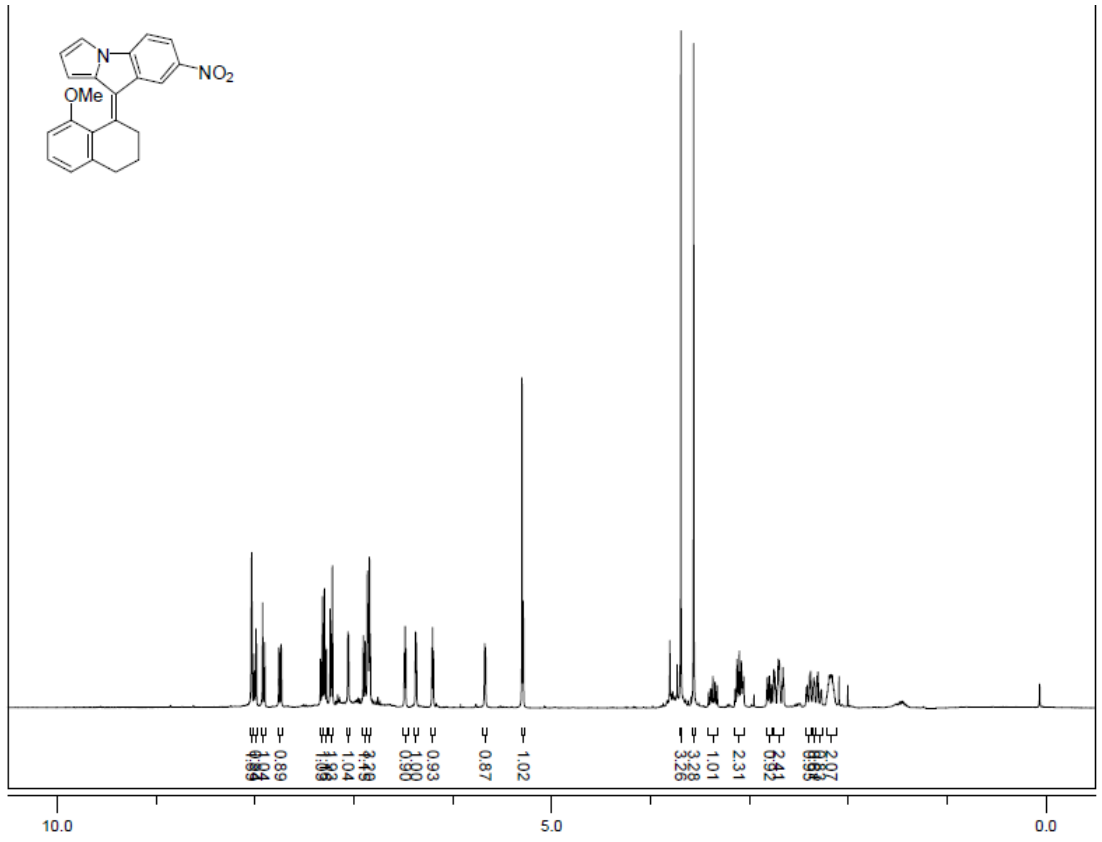
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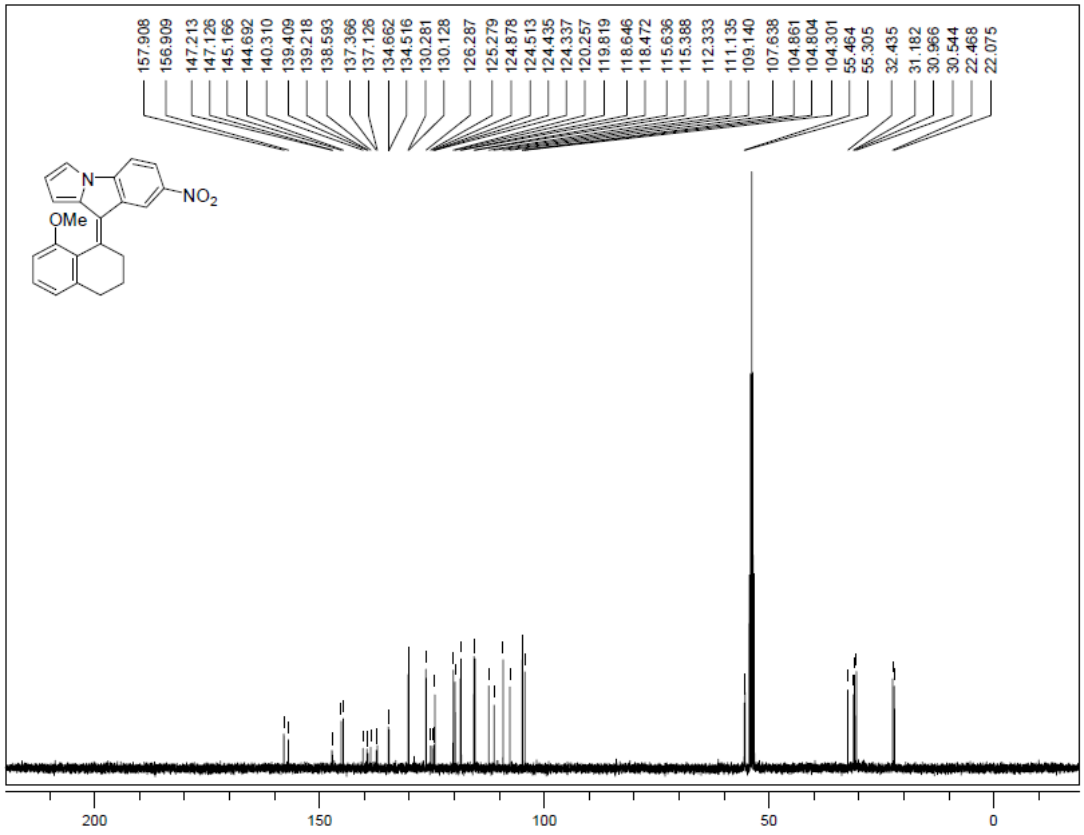
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NO2
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150
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50
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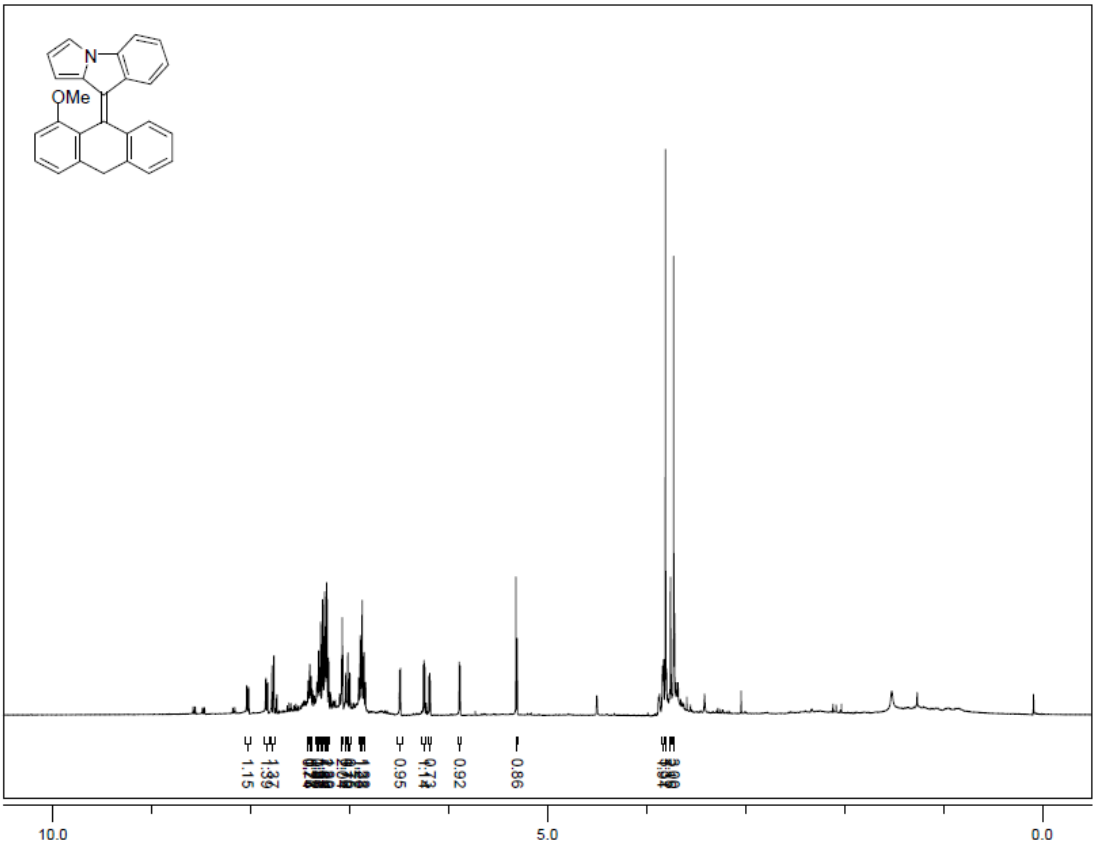
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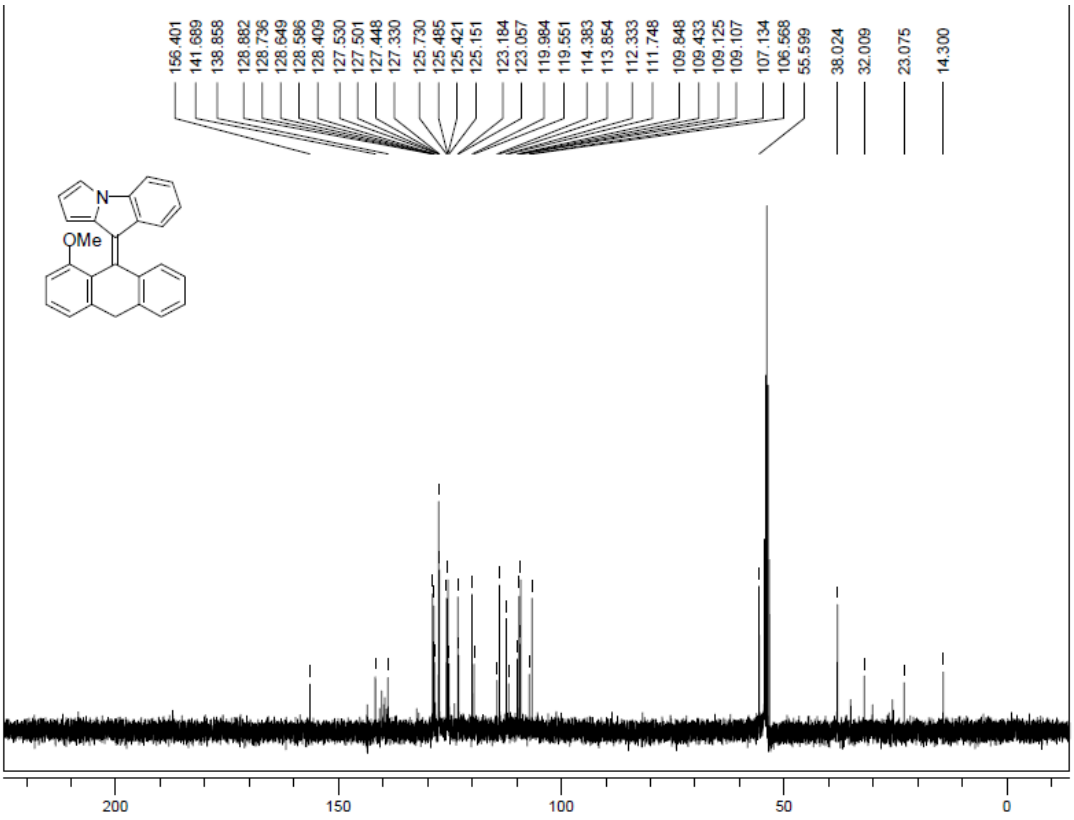
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OMe
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